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Haemodynamic Studies of the Eye.

Thomas Hardie Williamson, MBChB, FRCS, FRCophth.

1995

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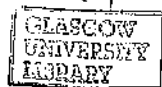


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Outline

The purpose of these studies was to investigate a new method of measuring the blood flow of the eye, namely colour Doppler imaging (CDI), and to use this method in an investigation of the pathogenesis of the condition of central retinal vein occlusion. The studies can be divided into two parts: chapters 1-7 deal with the examination of CDI in normal individuals and chapters 8-11 examine the use of CDI in the investigation of central retinal vein occlusion. In chapter 1, descriptions of other techniques used in the investigation of blood flow are provided and the current knowledge of the haemodynamic properties of the human eye are outlined, including changes associated with physiological variation and pharmacological effects. The haemodynamics of common ocular diseases and, in chapter 2, a summary of previously published colour Doppler studies of the eye are described. Our investigations assessing the technique are then presented.

In chapter 7 evidence is provided that blood viscosity has important effects on the haemodynamics of the eye and a study examining the interrelationship between blood flow and blood viscosity is described.

In Chapter 8 the reader is introduced to the condition of central retinal vein occlusion with descriptions of epidemiology, classification, aetiology, pathogenesis,

investigation, outcome and treatment. The condition is then studied using the colour Doppler technique and the results analysed with reference to the pathogenesis of the condition and to the use of CDI in the routine clinical investigation of the disease.

Chapter 11 examines the role of blood viscosity in the pathogenesis of CRVO.

In Chapter 12 the relationship between blood flow and viscosity in patients with central retinal vein occlusion is analysed, thereby allowing the description of a mechanism for the occurrence of the condition. Finally an overview of the findings from these studies is provided in Chapter 13 which ultimately examines the potential for further study and the possibilities for the use of therapeutic strategies in CRVO and the assessment of these strategies by colour Doppler imaging.

Summary

The study of the circulation of the eye has been taxing the imaginations of ocular investigators for 100 years, and has resulted in various and ingenious methods for its assessment. In recent decades technological advances have provided even more scope for examination. In these studies the method of colour Doppler imaging (which has considerably improved the localisation and measurement of blood flow in small blood vessels) was investigated as a means of examining the haemodynamics of the eye.

The examination of 95 normal individuals showed that many orbital blood vessels could be examined but that only the Doppler recordings (blood velocities and resistive index) from the ophthalmic artery, central retinal artery and vein were reproducible. Normal ranges for the Doppler measurements from these vessels were defined. The results were influenced by the age of the patient, by systemic blood pressure and by smoking habit. The identity of individual blood vessels was confirmed by examining patients with occlusive vascular disease.

According to the Hagen Poiseuille law an increase in the viscosity of a fluid reduces its flow. In a group of normal individuals the interrelationship between blood velocity (from colour Doppler imaging) and systemic blood viscosity was examined. No effect of

viscosity on the blood velocities was found but a negative correlation between viscosity and resistive indices (a Doppler measure of resistance to flow) was detected. This result suggested that in normal individuals there was compensation for increased blood viscosity by a reduction in peripheral resistance thereby maintaining blood flow to the eye.

The method of colour Doppler imaging was then applied to the examination of a 80 patients with central retinal vein occlusion in whom significantly reduced blood velocities were found in the retinal vessels. In fact the values of the velocities (a minimum peak velocity in the central retinal vein of less than 3.0 cm/sec) could be used to predict the development of the blinding and painful complication of iris neovascularisation^{potentially}.

Investigation of the systemic blood viscosity in these patients revealed elevated viscosity compared to population based controls and the examination of haemostatic factors demonstrated a thrombotic tendency particularly in those who developed iris neovascularisation. In contrast to normal individuals, the orbital blood velocities from the patients with central retinal vein occlusion were negatively correlated with their blood viscosities whereas resistive indices were unaffected, indicating that a reduction in peripheral resistance did not occur. In these patients therefore

not only was blood viscosity elevated but there was no evidence of compensation for this by reduction of peripheral resistance. Potentially therefore retinal blood flow is reduced in eyes with central retinal vein occlusion by increased blood viscosity and poor vascular compensation to such an extent that "occlusion" of flow in the vein occurs.

Dedication

To my family.

Quotation

"The world is as it is: men who are nothing, who allow themselves to become nothing, have no place in it."

V. S. Naipaul, from *A Bend in the River*.

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I am particularly grateful to the patients and volunteers whose cooperation has allowed me to perform these investigations and without whom these studies

would have been impossible.

Preface.

The inadequacy of our understanding of the condition of central retinal vein occlusion first became obvious to me when two patients presented with blinding and painful neovascular complications from the condition. My knowledge obtained from the standard texts lead me to believe that such complications should be rare and begged the question:

Why was fluorescein angiography unable to determine the risk of neovascular complications which could then be avoided by the application of prophylactic photocoagulation?

Around the same time I was using the technique of colour Doppler imaging to study the effects of topical Timolol on the ocular circulation. I had approached this method with some scepticism because of the considerable difficulty in recording the subtle changes of beta blockade on the small sized vessels of the eye. To my surprise our results revealed a detectable change and my interest was aroused. Little was known about the technique but the potential application of the method for the examination of retinal vein occlusion became obvious. This lead to the design and pursuit of the projects which are presented.

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1 Chapter1

OCULAR BLOOD FLOW MEASUREMENT.

1.1SUMMARY.

A critical review is provided of the currently applied methodologies for the measurement of blood flow in the eye in experimental circumstances and in the human. The haemodynamics of the normal human eye is outlined with reference to blood flow in different regions of the eye, autoregulation and the responses of the ocular circulation to changes in systemic blood pressure, pO_2 and pCO_2 , posture and intraocular pressure. The often conflicting results of studies examining the influences of topical pharmacological agents upon the eye's circulation are examined and the findings of the latest studies of the effects of ocular disease on ocular blood flow presented.

1.2 INTRODUCTION.

Many techniques have been devised to measure the haemodynamics of the human and animal eye. In this chapter these are outlined and their use in ophthalmological investigation summarised. Some have exploited the ability of an observer to visualise the retinal vasculature by optical means, others have been designed to study the haemodynamics of the invisible parts of the eye such as the choroid, optic nerve head and ciliary body. Although useful in ophthalmic investigation, none has satisfied all of the requirements of the researchers in this field and most have not achieved regular use in clinical practice. In any examination of blood flow a multitude of parameters must be studied (table 1.1). The interrelationship of these parameters must be determined whilst considering physical or physiological principles (table 1.2) which are often not strictly applicable to the vasculature, eg., the Hagen Poiseuille law was described for a rigid tube and not for elastic walled tubes such as blood vessels. In the human, study of the circulation is further hindered by the requirement for a noninvasive and safe method for obtaining measurements. Even so, study of the haemodynamics must be performed if we are to understand the mechanisms leading to the large variety of vascular diseases which affect the eye.

Table 1.1

Haemodynamic Measurements
Vessel length
Vessel Cross-Sectional Area
Blood Pressure
Blood Flow
Pulsatile flow
Intraocular pressure
Vessel Wall Tension
Resistance to flow
Blood Viscosity
Turbulence
Critical Closing Pressure

Table 1.1. Some of the measurements which might be required to allow an assessment of the haemodynamics of the ocular circulation.

Table 1.2. Physical and Physiological Principles in Blood Flow.

Flow (Q) = Velocity x Cross Sectional Area

Ohm's Law
$$Q = \frac{\text{Pressure difference}}{\text{Resistance}}$$

Reynold's number(R)
(Turbulence)
$$(R) = \frac{p2rV}{n}$$

Hagan Poiseuille Law
$$Q = \frac{(Pa-Pb) \pi r^4}{L 8 n}$$

$$\text{Resistance} = \frac{L 8 n}{\pi r^4}$$

Laplace's Law
$$\text{Trans Mural Pressure} = \frac{\text{Wall Tension}}{r}$$

p = density of the fluid
r = radius of the tube
V = velocity of the fluid
n = viscosity of the fluid
Pa - Pb = pressure difference
L = length of the tube

Bernoulli's Principle: A constriction of a vessel causes a conversion of pressure into kinetic energy thereby increasing the velocity and decreasing the pressure of the fluid in the vessel.

Doppler Equation
$$V = \frac{Df c}{2 F_o \cos A}$$

V = velocity
Df = Doppler frequency shift
c = Propagation frequency
Fo = Transmit frequency
A = Angle of incidence of Doppler beam to direction of flow

The blood flow to the eye is of particular interest because:

1. Many localised and systemic disorders affect the vasculature of the eye.
2. The eye has unusual haemodynamic properties because the tissues are subjected to a high intraocular pressure.
3. Ocular blood flow is autoregulated for example during changes in retinal illumination, blood pressure or posture.
4. Pharmacological agents which are routinely used in systemic and ocular diseases may affect the blood supply of the eye.

1.3 TECHNIQUES FOR THE MEASUREMENT OF OCULAR BLOOD FLOW.

Many ingenious and varied techniques exist for the measurement of ocular blood flow but some are restricted to experimental studies on animal models because of their destructive or invasive nature. For example, unlabelled or radioactively labelled microspheres in cats ^{292,294}, dogs ²⁵⁶ and monkeys ^{1,2,72} may be injected into the left ventricle of the heart and, after the animal is sacrificed, histological or radiographic measurement of the density of the microspheres is performed to allow an estimation of blood flow. Dye enclosed within heat labile liposomes has also been used to examine flow in localised areas of the retina ^{128,129,308} and involves an intravenous injection and release of the dye from the liposomes using laser light of the appropriate wavelength. The velocity of the dye as it passes through the vessel is recorded allowing a calculation of flow if the diameter of the vessel is measured. Radioactive tracers and radiography have also been employed, eg., ¹⁴C-iodoantipyrine has been used to estimate optic nerve blood flow in cats ²⁹². By cutting a hole in the sclera blood velocity measurements have been taken from the retinal circulation ⁶³. The Fick principle using nitrous oxide concentrations in uveal blood samples has also been employed ²¹⁴.

These methods are invasive and not applicable to the investigation of the human for obvious reasons. The minimally invasive procedure of fluorescein angiography remains the mainstay of clinical vascular investigation and has resulted in a number of techniques for the estimation of retinal blood flow. In particular, the time required for the dye to pass through the circulation has been estimated. Dye dilution curves produced from the intensity of the fluorescence in the retinal vessels have been calculated ¹¹⁰, more recently employing videoangiography and computerised image analysis ^{140,304}. Two curves of the intensity of fluorescence are plotted against time, for example from a retinal arteriole and an adjacent venule, figure 1.1, and the time delay between these two curves measured at various intensity levels of the dye, eg., at 0%, 25%, 50%, 75% and 100% of the peak fluorescence ¹⁴³. The time delay between the passage of dye is presumably inversely proportional to the blood flow rate through the retinal vessels therefore providing a measure of the retinal haemodynamics.

The temporal resolution of the scanning laser ophthalmoscope can be exploited to allow measurement of macular blood velocities from fluorescein angiography ^{5,207,268}. This is performed by injecting a bolus of dye and measuring the velocity of fluorescent white blood cells or gaps in columns of red blood cells as

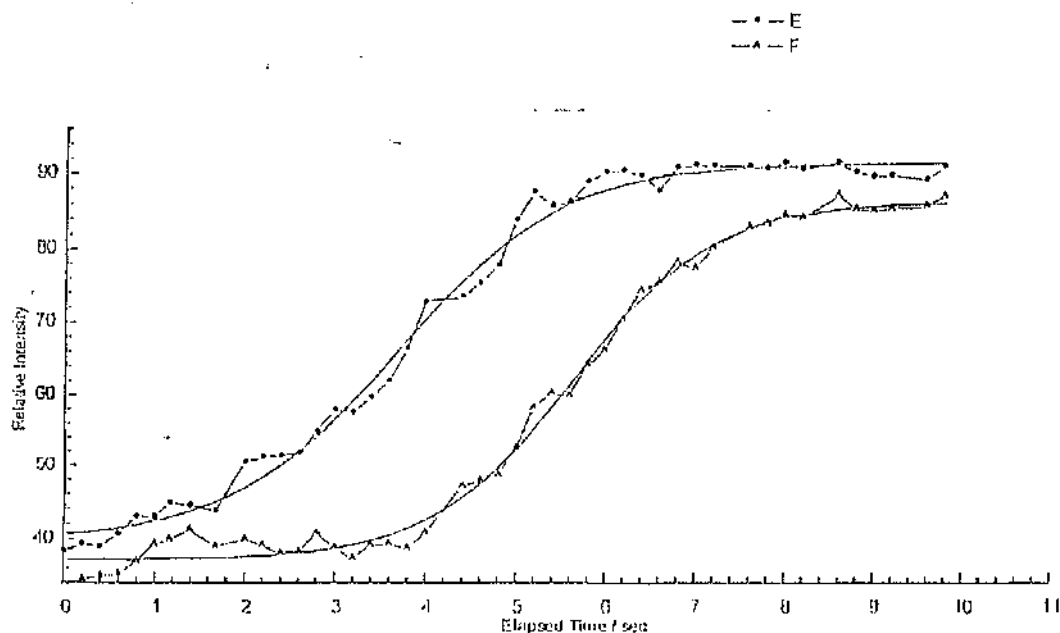


Figure 1.1. The dye bolus intensity curves from a fluorescein angiogram of an adjacent retinal arteriole (E) and venule (F) are shown from a patient with central retinal vein occlusion. The delay between the two curves provides a measure of the rapidity of the flow through the retinal circulation.

they pass through the perifoveal capillaries. These may be travelling at different speeds dependent on the orientation of the vessel, therefore multiple gaps or cells must be measured to provide an assessment of mean velocity in the capillaries. The capillary diameters are too small to be measured and therefore the flow in the vessels cannot be estimated from these velocities. It is also uncertain whether the rate of flow of the leucocytes which may stick to the endothelium of the capillaries, particularly in disease processes, is the same as the erythrocytes or plasma.

The pattern of flow in the choriocapillaris can be observed by using videoangiography and intravenous injection of indocyanine green ⁵⁷. This requires video recordings of 15 or 30 frames per second and digital subtraction of sequential frames to show the change in fluorescence in the blood vessels of the choroid. The rate of change of fluorescence in the choriocapillaris is faster than in the underlying blood vessels so that the images produced primarily show the changes in the capillaries.

Many studies examining the blood flow in the retinal circulation have been performed with bidirectional laser Doppler velocimetry (BLDV) which measures the velocity of blood in the intraocular retinal circulation by detecting the frequency shifts in laser light caused by the flow of erythrocytes ²³¹. The Doppler principle is applied, ie., the change in frequency of

the waveform is proportional to the velocity of the object. Often the results are averaged over measurement times of a few seconds to provide mean blood velocity. The measurement of the diameter of retinal arterioles or venules from monochromatic fundus photographs thereafter allows estimation of the blood flow from the formula:

$$\text{Blood Flow} = \frac{\pi \times \text{Diameter}^2}{4} \times \text{Mean velocity}$$

Estimation of total retinal volumetric flow in this way requires measurements of each major branch of the central retinal artery and vein. Although estimation from one branch alone may correlate well with total retinal blood flow in healthy subjects this is unlikely to be the case in disease where areas of the retina are often disparately affected. Reproducibility from the retinal arterioles is poorer than from the venules, probably because the short examination interval of a few seconds results in error from the pulsatility of the arteriolar blood flow. The technique may be difficult to perform because of a susceptibility to error from saccadic eye movements and requires specialised equipment which has confined its use so far to the research laboratory. Recently laser Doppler velocimetry has also been applied to the measurement of choroidal ²²⁸ and optic nerve head blood flow ²³² in

animals.

Another method employing laser light to estimate retinal blood flow is the laser speckle phenomenon 266,267. The scatter of laser light caused by movement of an object is proportional to the velocity of the object. Measurement of the scatter from a retinal vessel allows an estimation of the velocity of the blood cells in the vessel. This technique may be useful for the estimation of capillary flow but as yet has not been extensively investigated.

Any determination of blood flow by visualisation of the retina, eg., by fluorescein angiography, bidirectional laser Doppler velocimetry or laser speckle phenomenon, requires the use of mydriatics in most circumstances. These agents by their sympathomimetic or anticholinergic actions may affect blood flow. In addition, any system which requires the measurement of the diameter of retinal blood vessels requires adjustment of those measurements for the refractive error, axial length or keratometry of the eye. Correction factors have been devised by Littman 163,164 and Bengetson 12 but their accuracy has recently been questioned 6. If serial measurements are being used and absolute blood flow values are not required then a measurement of the distance between the disc and the fovea may be used to standardise the magnification of photographs of the same individual 184. The use of light to examine the retina can also affect the blood flow which may vary

after short durations of retinal illumination and dark adaptation ¹¹².

Blood velocities in the macular capillaries are assessable by nonoptical means using the blue field entoptic phenomenon, appreciable if we look at a deep blue sky ^{233,253}. This method presents a diffuse blue light (430nm) to one eye of a subject allowing visualisation of their own white blood cells in their macular capillaries (seen as multiple white "comma" shaped flecks momentarily crossing the paracentral visual field). The density and velocity of these are matched by the subject to the density and velocity of spots on a VDU screen which is observed simultaneously with the other eye. The system therefore requires the cooperation of the subject, good vision and introduces an unavoidable subjective component.

A number of methods have been devised for the estimation of the pulsatile component of total ocular blood flow from the variations that occur in intraocular pressure with the systemic pulse ^{152,252}. These variations in pressure can be measured by tonography, figure 1.2, and have been related to volume changes in cadaver eyes allowing extrapolation of the intraocular pressure changes to variations in blood volume with the systemic pulse. Such an extrapolation may however be inaccurate when the size of the eye or the ocular rigidity is changed, eg., in myopia ^{141,152}. Several

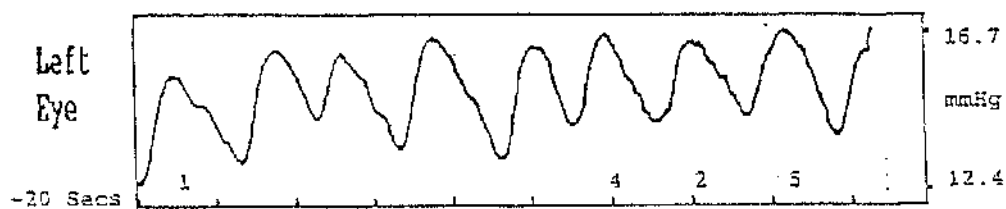


Figure 1.2. A tonography tracing is shown, illustrating the variations in the intraocular pressure from which the pulsatile flow in the eye (mostly choroidal) can be estimated.

assumptions which must be applied with these techniques have been outlined ^{113,252}: 1. The change in intraocular pressure is related to the change in volume induced by the flow of blood into the eye with each pulse. 2. Retrograde blood flow does not occur. 3. The outflow of blood is constant and nonpulsatile. 4. The formulae for the calculation of pulsatile blood flow from the pressure changes are valid. 5. The blood vessels do not collapse ¹⁴⁴. Furthermore, pulsitometry measurements only detect the pulsatile component of blood flow, the nonpulsatile component is not measured. Furthermore the relationship between pulsatile and total blood flow is unclear.

In oculo-oscillo-dynamography a tonometer and suction cup are applied to the sclera of the eye ²⁸⁰. The intraocular pressure is raised and changes in the waveform from tonometry are interpreted to indicate cessation of flow in the retinal and choroidal vasculature allowing, it is claimed, measurements of retinal and choroidal pulse pressure. The rise in intraocular pressure results in the undesirable side effect of obscuration of vision when systolic retinal blood pressure is reached and the use of the scleral suction cup also introduces an invasive component which may induce unphysiological circumstances such as ischaemia on the eye which may alter its blood flow. The effect of the suction cup in raising intraocular pressure may be altered by the size of the eye as has

been shown to occur with ocular pneumoplethysmography, a similar technique employing a pneumatic tonometer ⁷⁰.

1.4 BLOOD FLOW IN THE NORMAL EYE

Total human ocular blood flow is estimated to be approximately 1 ml/min, most of which supplies the vasculature of the uvea (primarily the choroid), only 2 to 5% supplying the retina ¹¹¹. The eye is supplied by the ophthalmic artery, in this vessel blood pressure is estimated to be 2/3 of brachial blood pressure. The perfusion pressure of the eye is however less than this because the intraocular pressure is 10 to 21 mmHg. A formula has been used to estimate mean ocular perfusion pressure:

$$\text{mean OPP} = 2/3(\text{DBP} + 1/3(\text{SBP} - \text{DBP})) - \text{IOP}$$

OPP = Ocular Perfusion Pressure

DBP = Diastolic Blood Pressure (Brachial)

SBP = Systolic Blood Pressure (Brachial)

IOP = Intraocular Pressure

The blood flow to the eye is pulsatile and induces intraocular pressure variations from which the mean pulsatile component of the blood flow to the eye has been estimated at approximately 0.724ml/min ¹⁵².

In the human, the retinal circulation has a mean flow of 0.033ml/min ²³¹. In the retinal arterioles blood flow probably exhibits a shearing core with blood

flowing at a uniform rate centrally and more slowly peripherally and conforms to the principles of an end artery system with equal flow in the retinal arterioles and venules ¹¹¹. Regional differences in the retina exist with higher flow in the vasculature of the temporal region than the nasal region, reflecting the increased retinal area supplied by the temporal vessels and the increased metabolic activity of the macula ¹¹¹. The mean blood velocity in the arterioles is higher than in the venules because the diameter of the intraocular retinal arterioles is less than the retinal venules. In the retina autoregulation of blood flow exists, probably as a local response of the vessels to metabolites from the retinal cells. The role of the autonomic nervous system is uncertain for although autonomic receptors have been detected in the retinal blood vessels in their extra-ocular course, they are thought to be absent from the intraocular retinal circulation ¹⁸.

In the uveal tissues autonomic receptors are present and blood flow can be altered by manipulation of the autonomic system, eg., stimulation of the sympathetic system reduces blood flow whereas cervical sympathectomy causes an increase in flow ²⁹³. In contrast to the retinal circulation autoregulation of blood flow probably does not occur in the choroid, possibly because the choriocapillaris separates the choroidal arterioles and venules from the retina and therefore

from its metabolites ¹⁸. The high blood flow and low utilisation of nutritive substrates in this circulation may also reduce the effect of retinal metabolism. The difference in the responses of the retinal and choroidal circulations is evident when ocular perfusion pressure is reduced, resulting in reduced choroidal blood flow whilst retinal blood flow remains stable ¹⁸. The choriocapillaris fills first at the macula and then in the periphery ⁵⁷.

Blood flow in the eye can be affected by both systemic and ocular factors. Changes in posture should be expected to alter the perfusion pressure in the ophthalmic artery pulse pressure but this varies only by 10mmHg or less when standing ¹⁵². The confusing relationship of pulsatile blood flow in the eye to total blood flow is highlighted by the reduction in pulsatile blood flow of 27.5% on the assumption of the supine position in healthy volunteers despite a rise in the perfusion pressure ²⁷⁶. Retinal blood velocities are stable during postural changes despite alterations in perfusion pressure ³⁰¹ and flow is effectively autoregulated during increased systemic blood pressure from isometric exercise until mean brachial artery blood pressures reach 115 mmHg after which the blood flow increases ²³⁴.

Evidence that autoregulation in the retinal circulation is controlled by metabolites has been provided by the

observed responses to hyperoxia or hypercapnia ⁹⁶. In one study, retinal arteriolar vasoconstriction and venular dilation were observed after high concentration oxygen breathing but no change was detected with variation of blood CO₂ levels ¹¹². Dilation of the retinal blood vessels and shortening of fluorescein dye transit times have, however, been detected in monkeys with increasing arterial pCO₂ ²⁷⁹ and more recently in humans ⁹⁶. In the macular circulation during isocapnic hypoxia blood velocities have been found to increase by 38% (the diameter of the arterioles and the venules increased by 8.2% and 7.4%, respectively), whereas hyperoxia reduced the velocity by 36% (the diameter of arterioles and the venules reduced by 5.6% and 10% respectively) ⁵³. These variations were unexpectedly large considering the small rise in blood oxygen content that can be induced by hyperoxia (oxygenised haemoglobin does not rise significantly). In recent studies performed with scanning laser ophthalmoscopy, changes in blood velocity (10% variation) were found to be more in keeping with the expected changes associated with isocapnic hyperoxia and hypoxia ⁹⁶. The changes in the diameter of the larger retinal vessels are believed to be too small to account for the changes in blood flow seen with such alterations in oxygen concentration ²³⁰. As elsewhere in the body, it is postulated that the smaller retinal arterioles and venules contribute most to the regulation of blood

flow.

Raised intraocular pressure causes a reduction in blood flow to the anterior uvea, choroid and retina ²⁹⁴. The retinal blood flow is however autoregulated up to intraocular pressures of 30-34 mmHg after which the perfusion decreases whilst intraocular pressures lower than 10 mmHg cause the retinal blood flow to increase ^{230,294}. With high intraocular pressures the perfusion of the eye continues until the pressure reaches 6 mmHg below the perfusion pressure of the blood in the ophthalmic circulation, at which point the critical closing pressure of the ocular vascular bed is reached and blood flow ceases ¹⁶.

The effect of illumination of the retina has been investigated by a number of techniques. In animal models, flickering light increases the retinal blood flow whereas constant illumination reduces retinal blood flow ¹⁸. In humans increases of 65% in retinal blood velocity, 5% in venular diameter and 82% in calculated blood flow rate have been reported in the first seconds after dark exposure ²³⁰ with peak measurements reached after 5 minutes dark adaptation when the velocity in the venules was 47% higher than light adapted levels. In another study of the retinal arterioles increases in blood velocity of 40-55% were detected with negligible dilatation of the arterioles of 2 to 3% and increases in the calculated flow rate of

40-70% ⁸⁴. In contrast no change in blood flow in the choroid with dark adaptation was found using infrared absorption cineangiography with indocyanine green ¹¹². Measuring the response of the retinal blood flow to dark adaptation may provide a means of assessing the autoregulatory capacity of the retina and may be used in the investigation of conditions such as diabetes.

1.5 BLOOD FLOW MEASUREMENTS IN OCULAR PHARMACOLOGY.

A number of topical and systemic medications may influence the blood flow to the eye and have particular relevance, therefore, to different disease processes such as diabetes, glaucoma, systemic hypertension and ocular vascular occlusion. Beta blockers and sympathomimetics may affect blood flow because an imbalance is produced between the influence of the alpha and beta sympathetic receptors on the ocular vasculature. The effect of this imbalance has often been difficult to ascertain and differing results have been found in various studies. Even though these agents can affect various measurements which are relevant to blood flow it is often difficult to determine whether these effects are beneficial or detrimental to the eye. The effects of the agents upon systemic blood pressure, intraocular pressure and the untreated fellow eye often confound the interpretation of the results. For example, the contralateral eye has

often been used to apply placebo drops, this however does not take into account the systemic absorption of the active agent nor the interrelationships which may exist between eyes for the control of intraocular pressure.

The imbalance of sympathetic stimulation induced by medications may cause changes in blood vessel calibre. Indeed vasoconstriction has been detected in the ocular circulations with both sympathomimetics and beta blockers. For example, vasoconstriction was produced in the ciliary body after instillation of topical phenylephrine hydrochloride, timolol maleate and betaxolol hydrochloride into rabbit eyes ²⁸¹.

Tolerance developed to betaxolol and partially to phenylephrine after seven weeks of administration of the drugs. In humans, Martin and Rabineau detected vasoconstriction of the retinal arterioles with timolol in serial examinations of monochromatic fundus photographs ¹⁸⁴.

It is usually the expectation that vasoconstriction will decrease flow. This has occurred with the use of adrenaline which has produced a reduction of blood flow to the iris and ciliary processes of rabbits ⁷⁹ and in monkeys ¹ in investigations using microsphere techniques. With beta blockers often no changes in blood flow have been detected. For example, a cross over study using a single instillation of timolol,

betaxolol, and levobunolol in normal subjects failed to find any changes in perimacular haemodynamics (measured by blue field entoptic simulation) in normal subjects compared to a placebo condition ⁹⁸. Similarly, Green using radioactively labelled microspheres to examine topical therapy on rabbit eyes found no effect on blood flow with timolol (or with noradrenaline, ecthiopate iodide or pilocarpine)⁷⁹. Studies employing tonography have shown no effect of timolol on pulsatile ocular blood flow in normal individuals ²²¹ and in glaucoma patients ²⁷⁵ and Grunwald has detected no effect of carteolol on blood velocity, volumetric flow rate or venous diameter in the retinal circulation using laser Doppler velocimetry ⁸⁴. Another study using the latter method however detected an 11% increase in the maximum velocity of red blood cells in the retina and 13.2% of estimated blood flow in timolol treated eyes ⁸² and a similar effect has been found in patients with ocular hypertension ⁸³. If agents which lower intraocular pressure such as beta blockers cause vasoconstriction, this may be a response to lowered intraocular pressure and not a direct effect of the drug on the blood vessels. Vasoconstriction may occur to compensate for the increased perfusion pressure resulting from lowered intraocular pressure, thereby stabilising the blood flow. Studies employing techniques which can estimate the blood pressure in the ocular vessels have not always detected such changes in

perfusion pressure. For example, using compression ophthalmodynamometry, although mean blood pressure in the ophthalmic artery was increased in timolol treated eyes compared to the "placebo treated" contralateral eye, multiple other parameters, such as diastolic and systolic blood pressure and serial measurements of blood pressure in the ophthalmic artery were unchanged⁸⁵. Pullinatt in a parallel comparison of normal individuals using oculo-oscillo-dynamography found no change in retinal or ciliary perfusion pressures with timolol, betaxolol, pilocarpine and acetazolamide despite reductions in intraocular pressure²²⁰. Carteolol even showed a significant reduction in perfusion pressure in this study.

The topical application of the alpha agonist aproclonidine which might be expected to cause vasoconstriction has produced no acute effects on macular blood flow on blue field simulation in normal subjects after single dose topical administration¹⁸⁰.

Intravenous acetazolamide has been shown to cause vasodilation and increased retinal blood velocities (laser Doppler velocimetry) in normal volunteers²²³. A carbonic anhydrase inhibitor, this agent causes an increase in tissue pCO_2 which may have induced vasodilation of the retinal vessels. In combination with the increased perfusion pressure from reduced IOP and the measurement of increased blood velocities it

would appear highly likely that increased blood flow occurs with the drug. This may be usefully exploited to increase blood flow in conditions such as central retinal artery occlusion.

The effects of other agents have been investigated primarily in experimental circumstances using animals models. For example, dopamine antagonists have been shown to increase pulsatile blood flow in the eyes of rabbits whilst reducing intraocular pressure ⁵⁷. In the same study dopamine and bromocriptine had no effect on flow. Anticholinesterase inhibitors have reduced the flow detected in the anterior uvea in rabbits (microspheres method)²⁵¹. Further investigations of the effects of drugs may be stimulated by recent investigations of the effects on the ocular circulations of endothelin-1 and nitric oxide which are derived from vascular endothelial cells, the former causing vasoconstriction and the latter vasodilation ^{77,78}.

Although considerable efforts have been made to examine the potential effects of drugs on ocular blood flow the clinical relevance of the findings is as yet unclear, particularly with topical medications such as beta blockers. Studies should be examined carefully for methodology before the conclusions are accepted.

1.6 BLOOD FLOW AND OCULAR DISEASE.

Ocular and systemic diseases have been investigated using various techniques for examination of ocular blood flow but few are applied in the clinical setting. There are however diseases in which the measurement of blood flow might aid diagnosis and management. In diabetic retinopathy retinal blood flow may be reduced and the normal autoregulatory capacity deficient ^{88,256}. Small induced diabetes in dogs and noted that retinal blood flow was significantly reduced after 5 months, using a radionuclide labelled microsphere technique ²⁵⁶. Grunwald using laser Doppler velocimetry, investigated diabetic patients with poorly controlled blood glucose and, in comparison to normals, found that the autoregulatory response to oxygen breathing (ie., decreased retinal blood flow) was less in diabetic patients ⁸⁸. A mean 15% increase in retinal blood flow during hyperglycaemia compared to normoglycaemia (after administration of insulin) was found in poorly controlled type 2 diabetic patients examined by laser Doppler velocimetry ⁸⁷. The autoregulatory response to oxygen breathing was reduced during hyperglycaemia in these patients. A reduction in mean retinal venous diameter, red blood cell velocity and volumetric blood flow (from laser Doppler velocimetry) has been detected after panretinal photocoagulation with a return of the autoregulatory

response to oxygen breathing ^{54,86}. Reduced choroidal blood flow in diabetic patients has been suggested by the observation of a mean pulsatile ophthalmic artery blood flow (from ophthalmodynamometry) of only 0.15 ml/min ¹⁵². It therefore appears that blood flow in the eye may be reduced in patients with diabetic retinopathy particularly in the retinal circulation. Those with poor control may have a relative increase in blood flow which is then reduced by tightening glucose management. Whether clinically applicable methods of blood flow assessment can be used in monitoring the progress of diabetic retinopathy and responses to treatment remains to be seen.

Ocular hemodynamics are altered in patients with glaucoma and ocular hypertension but the methods of studies must be examined to ensure that topical medications have been stopped (because of their potential effects on blood flow) with adequate washout periods employed. Of course, if the patient is off treatment, blood flow changes may merely reflect the presence of raised intraocular pressure and not primary vascular abnormalities. With these caveats in mind, studies of patients with chronic open-angle glaucoma have found prolonged dye transit times on fluorescein videoangiography ^{264,303} and reduced ophthalmic artery velocities by duplex Doppler ultrasound ²³⁵. More severe loss of visual function in glaucoma has been

associated with reduced white blood cell velocities in the macula (and presumably reduced macular blood flow) using blue field simulation ²⁶². The alterations in blood flow were most likely to have resulted from the intraocular pressure drop from the operation but the measurements may also have been influenced by the fact that most of the patients were on topical medications such as beta blockers pre-operatively but not post-operatively.

To avoid the problem of raised intraocular pressure Trew compared the results of ophthalmodynamometry in patients with ocular hypertension to patients with primary open angle glaucoma ²⁷⁶. The patients with glaucoma had a lower mean pulsatile ocular blood flow ²⁷⁵. Obviously patients with normal tension glaucoma do not have the confounding influence of raised intraocular pressure. Reduced pulsatile blood flow from ophthalmodynamometry has also been detected in such patients ¹²¹. Whether the reduced blood flow in glaucoma is contributing to the pathogenesis of the disease or is secondary to the loss of nerve fibres in the disease remains as yet undetermined ¹²².

Cranial arteritis (often a clinically hazardous condition to manage) can cause profound haemodynamic changes in the orbit. Intraocular pulse pressure amplitude (the measure from which ophthalmodynamometry estimations of pulsatile blood flow are obtained) has been compared in patients with giant cell arteritis and

patients with nonarteritic anterior ischaemic optic neuropathy or nonarteritic central retinal artery occlusion ²⁰. The arteritic patients showed a mean pulse amplitude which was only 37% of the mean value in the nonarteritic group (estimated values of pulsatile ocular blood flow of less than 0.6ml/min in the arteritic group). In another study using a pneumotonometer the mean ocular pulse amplitude was reduced in patients with ischaemic optic neuropathy and temporal arteritis but not in those with neuropathy alone or temporal arteritis alone ¹⁷. In this group, patients with ischaemic optic neuropathy and central retinal artery occlusion associated with temporal arteritis, also showed a reduced pulse amplitude in their contralateral eyes. Many of these patients' recordings increased after treatment with prednisolone therapy. In temporal arteritis the severity of the disease appears to be associated with more severe changes in blood flow therefore monitoring of blood flow should aid diagnosis and the determination of the response to therapy.

In central retinal vein occlusion blood flow has been shown to be reduced by fluorescein angiographic techniques ^{246,258}. Stenosis of the carotid arteries sometimes reduces the ocular blood flow although studies have revealed differing results ^{152,188,247}. Reduced pulsatile ocular blood flow has also been found

in cataractous patients, the relevance of which is unknown ¹¹⁶.

1.7 CONCLUSION

The measurement of blood flow in the eye is a complex and often confusing issue. No technique has reached the status of gold standard and all have disadvantages not least because of their measurement usually of only one of the multiple parameters involved in blood flow. Their collective application over many studies however has revealed patterns of haemodynamic change in normal physiology and in ocular diseases. As the technology and its application continues to improve, the shortfalls of current methods are gradually met. In the future, more of these methods may be available to the physician in the clinical setting.

2 Chapter 2

INTRODUCTION TO COLOUR DOPPLER IMAGING OF THE EYE.

2.1 Summary.

The technique of colour Doppler imaging is introduced and previously reported studies employing the method are described in this chapter.

2.2 Colour Doppler imaging, Previous Studies

Christian Andreas Doppler (1803-1853) was the first to describe the principle of using sound waves to measure the velocity of an object. The principle using ultrasound energy was first applied to the investigation of human diseases in 1957 and is now established in routine clinical practice ²⁴⁵. Although the investigation has previously largely been confined to the examination of the larger vessels in the body such as the carotid arteries and the heart, recent technological innovations and advances have allowed the inspection of other vascular systems.

At first, continuous wave Doppler ultrasound was used which had the disadvantage of recording signals from all of the vessels in the path of the ultrasound beam. With the development of B mode and duplex Doppler ultrasound, vessels at specific depths can be examined if their anatomical positions are known. Furthermore colour mapping of flow in colour Doppler imaging (CDI) has greatly facilitated the identification of blood

flow, particularly in vasculatures which are below the resolution of B mode scanning. This technique has aided the examination of structures of variable or complex vasculature, such as the neonatal brain ^{197,198}, testes ¹⁹⁵, and abdominal organs ¹⁵⁷ because flow in specific blood vessels can be identified on a visual display unit (VDU) screen. As yet CDI is qualitative and quantification requires the application of spectral analysis of the Doppler signals followed by angle correction calculations for blood velocity measurements.

Erickson was the first to describe the qualitative appearances of CDI in some normal orbits and in a few orbital disorders ⁵². More recently, blood velocities in the vasculature of the eye and orbit in normal healthy populations have been described using colour Doppler imaging ¹⁵⁸ (the fellow eyes of patients with choroidal melanomas) and duplex scanning ⁹⁰.

As the technology advances so the sensitivity of the machinery increases, currently most of the scanners available commercially detect flow rates as low as 1-3 cm/s ^{270,302}. Lower flow rates than this may be missed giving the examiner the false impression that a vessel is occluded. This error is increased when examining blood vessels of small diameter such as in the orbit but can be reduced by keeping the Doppler beam parallel to the direction of flow in the vessel. To provide

measures of the degree of pulsatility in the velocities measured by Doppler two indices have been used: resistive index ²¹⁷ and pulsatility index ⁷⁴. The pulsatility of the blood flow can then be interpreted to provide estimates of the peripheral resistance to flow in the circulation.

Imaging by ultrasound has been regarded as safe and non-invasive but as the resolution of modern ultrasound equipment increases so does the ultrasound energy being applied to the tissue. In colour Doppler imaging the highest Ispta intensities occur during spectral analysis of the Doppler frequency shifts. Ispta levels for the Acuson 128 during pulsed Doppler of 44 mW/cm² are below the maximum recommended levels advised by the British Medical Ultrasound Society (100mW/cm²) and the Food and Drug Administration of the USA (68mW/cm²). Considerably higher ultrasound intensities are required to induce damage to the choroid and lens of rabbits, approximately 100 W/cm². The occurrence of damage also depends upon the duration of the exposure to the ultrasound ¹⁶⁵⁻¹⁶⁷. In general the colour coding of blood velocity can be used to speed the localisation of a site of interest thereby shortening the exposure time.

The results of previous control populations using Doppler ultrasound to measure the orbital blood velocities are shown in table 2.1. The ophthalmic artery, central retinal artery and vein, posterior

Table 2.1

	Technique (Instrument)	(n)	OA (cm/sec)	CRA	CRV
Lieb	CDI (QAD 1)	40	31.4 (4.2)	10.3 (2.1)	2.9 (0.25)
Guthoff	Duplex (ATL Ultramark)	72	31.6 (9.0)	9.5 (3.1)	5.7 (1.25)

Table 2.1. Mean peak systolic blood velocity (and SD) in the major vessels in the orbit from two studies of Doppler velocimetry in normal eyes (n = number of subjects, OA = ophthalmic artery, CRA = central retinal artery and CRV = central retinal vein).

ciliary arteries, vortex veins and inferior and superior ophthalmic veins can all be detected (the normal arterial anatomy is shown in figure 2.1). The exact reproducibility of the recordings from these sites has not been fully determined. Measurements from the central retinal artery and vein and the ophthalmic artery appear to be reliable having been detectable in almost all normal orbits in the major series reported, so far ^{90,158}. The anteroposterior orientation of these blood vessels ^{99,103} in the orbit greatly aids accurate Doppler recordings because the calculation of blood velocities from the Doppler frequencies from a vessel are dependant upon the angle of incidence of the ultrasound beam to the direction of travel of the vessel (figure 2.2). Although blood velocity in the posterior ciliary arteries can be recorded the results show a wide range of values perhaps because of the tortuosity of these vessels ¹⁵⁸. Investigation of patients with known occlusion of the posterior ciliary or central retinal arteries may help determine the influence of these vessels on the Doppler recordings in this area.

As yet, changes in these Doppler measurements with age and posture have not been investigated. Elevation of the intraocular pressure (IOP) above 40mmHg caused a reduction in the measurements of blood velocity by duplex scanning in the central retinal artery ⁹⁰. This

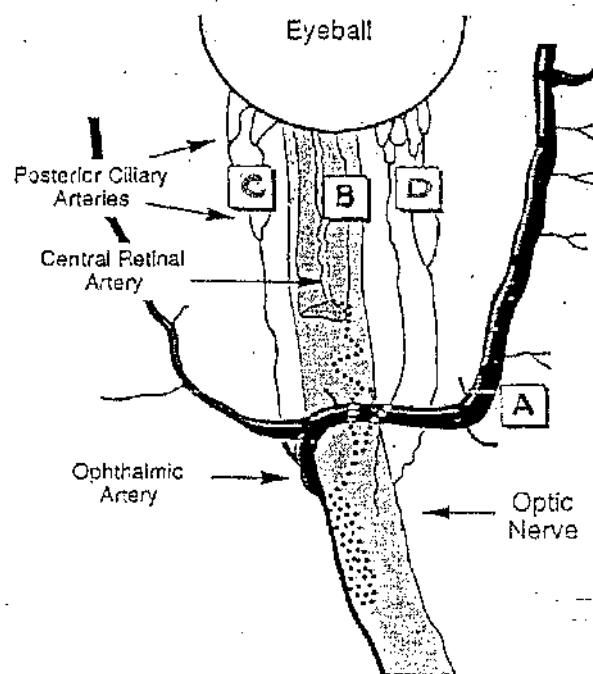


Figure 2.1 The normal arterial anatomy of a right orbit is illustrated showing the antero-posterior orientation of the blood vessels. The usual positions for the interrogation of the blood vessels by Doppler are indicated by A (ophthalmic artery), B (central retinal artery and vein), C (temporal posterior ciliary arteries) and D (nasal posterior ciliary arteries).

The Effect of Angle on Velocity Calculations

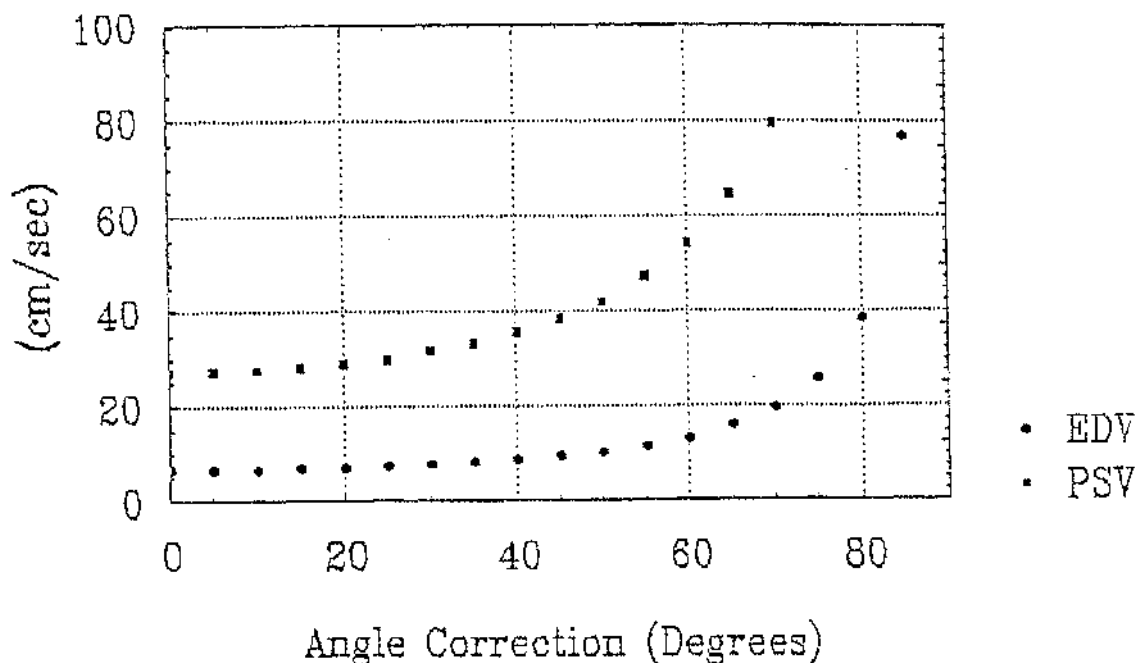


Figure 2.1. The variation in the calculation of blood velocities from the Doppler frequency shifts which can be induced by inadequate correction for the angle of travel of the ultrasound beam to the direction of blood flow. Considerable error is produced at angles above 45°.

is in accordance with the results of other investigative techniques of blood flow which have indicated that autoregulation of the retina fails above this level of IOP ²²⁹. The Doppler imaging technique by the application of a probe to the eyelid may raise the IOP thereby altering the blood flow to the eye. An investigation is required to determine the magnitude of IOP rises during ultrasound examination so that its possible effect on blood flow can be assessed. The technique has already been applied to the investigation of some ocular disorders. In 11 patients with severe carotid stenosis and ocular ischaemic syndrome, peak systolic velocity was significantly reduced to a mean of 3.5 cm/s in the central retinal artery and to 3.9 cm/s in the posterior ciliary arteries ¹¹⁵. In the ophthalmic artery of these patients reversal of flow was observed in 12 of the 16 eyes examined. A case of 100% internal carotid artery occlusion in a 24 year old man showed hypoperfusion of the central retinal artery and nasal posterior ciliary arteries on fluorescein angiography ¹⁵⁹ which correlated with undetectable flow in these vessels by CDI. The peak systolic velocity in the ophthalmic artery of only 9.1 cm/s was interpreted as signifying that there was partial occlusion in the ophthalmic artery of this patient. Blood flow returned to the ocular vessels after 3 weeks without any treatment of the carotid stenosis.

Reduced ophthalmic artery velocities in glaucoma have been found by duplex Doppler ultrasound ²³⁵ and colour Doppler imaging ⁶⁷. After treatment by trabeculectomy increased blood velocities and evidence of reduced peripheral resistance to flow have been detected in the central retinal artery and posterior ciliary arteries by colour Doppler imaging ²⁷⁷. The alterations in blood flow were most likely to have resulted from the intraocular pressure drop from the operation but the measurements may also have been influenced by the fact that most of the patients were on topical medications such as beta blockers pre-operatively but not post-operatively. A study of patients with normal tension glaucoma found increased vascular resistance in the ophthalmic arteries as compared to age-matched healthy control subjects ⁹⁷. The increased resistance was normalised when pCO₂ levels were elevated in the patients suggesting the presence of reversible vasospasm in these patients with normal tension glaucoma.

Examination of a case of superior ophthalmic vein thrombosis showed absence of flow in the dilated superior ophthalmic vein and flow in dilated collateral venous channels ⁵⁶ but the significance of this is unknown because the normal pattern of flow in the superior ophthalmic vein has not yet been defined. Three series of patients with intra-ocular tumours

examined by colour Doppler or a combination of colour Doppler and Duplex examination techniques have been published ^{91,161,305}. A tumour circulation was detected in almost all of the cases of choroidal malignant melanoma which have been described (figure 2.3). A few patients in whom no tumour circulation was detectable had raised intra-ocular pressures from secondary glaucoma and may have had secondary tumour necrosis from cessation of the tumour blood supply. The examination of Doppler frequency shifts of choroidal melanomas after radiotherapy has determined that the blood flow velocity rises in the first few days and then reduces significantly from predosage levels ⁹¹. Nineteen of the 20 cases described by Wolff-Kormann had reduced blood velocity as shown by CDI before tumour regression was detected by conventional ultrasonography ³⁰⁵. In one patient in whom increased velocity was noted after treatment tumour recurrence subsequently developed.

Other intraocular tumours such as choroidal haemangiomas and metastases have also shown evidence of tumour vessels when examined by CDI ^{161,305}. Haemangiomas have reportedly higher velocities than melanomas. Although a case of posterior hyperplastic primary vitreous showed blood flow in a vessel within its centre ²⁹⁶, other lesions which may mimic malignant tumours, such as age related macular degeneration, choroidal osteoma and choroidal naevi have shown no



Figure 2.3. The tumour vascular supply is detectable in this color Doppler image of a malignant melanoma. It may be difficult to determine the direction of travel of the vessel and so Doppler frequency shifts have often been quoted in studies of tumours without converting these to velocities.

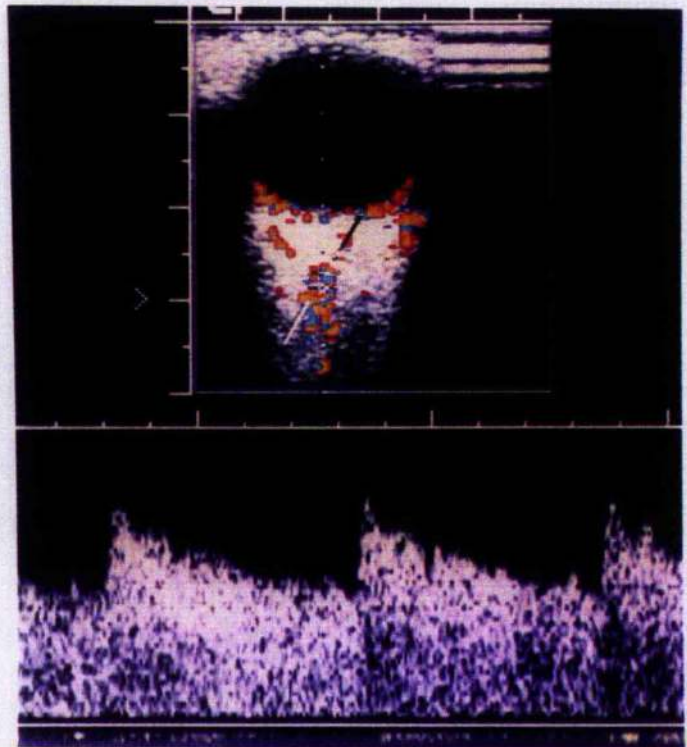


Figure 2.4. The dilated superior ophthalmic vein is apparent in the superior orbit of a patient with carotico-cavernous fistula showing an unusual arterial type of waveform on spectral analysis.

detectable blood flow 161,305.

Patients with carotico-cavernous sinus fistula show dilated orbital veins particularly the superior ophthalmic vein with a change from continuous venous flow to pulsatile arterial flow 13,52,55, an example is shown in figure 2.4. The direction of flow is usually reversed and in the vortex veins may be bidirectional 52. In one of the described cases the flow velocities returned to a venous pattern after embolisation of the fistula 55.

Reversal of flow in the superior ophthalmic vein has also been described in a case of thrombophlebitis of the cavernous sinus and in two cases of orbital apex tumour 13. CDI has also been used to examine an orbital arterio-venous malformation in which low resistance arterial flow was seen 52, orbital varices in which flow can be detected in the varix during the Valsalva manoeuvre as the vessel fills and empties 13,160, and a few cases of orbital tumours 120.

The description of a case of gaze induced amaurosis fugax secondary to an intraconal orbital mass further illustrates the potential of CDI to elucidate the pathogenesis of vascular disease processes 136. The peak systolic flow velocity in the central retinal artery was reduced in this patient from 11.6 cm/s to 5.0 cm/s during abduction of the eye when amaurosis fugax occurred signifying a partial occlusion of this

vessel during eye movements. As yet the gaze induced changes in the blood velocity measurements are not known for the normal population.

There is great potential for the use of CDI for investigating the effects of pharmacological agents on blood flow to the eye because it is a noninvasive method accommodating repeated examinations. Our study investigating the use of topical timolol 0.5% detected a significant reduction in the resistive index in the administered and fellow eyes, indicating a reduction in the resistance to flow. This appeared to be independent of the effect of the drug on IOP, systemic pulse and blood pressure and may have been due to an effect of the drug on the retinal blood vessels themselves, perhaps indicating that contrary to current opinion sympathetic receptors may be present on these vessels. Colour Doppler imaging of patients after administration of aproclonidine have shown a reduction in end diastolic velocities from the posterior ciliary circulation suggesting reduced peripheral resistance to flow ¹⁷⁹.

The Doppler principle has been used primarily for the investigation of blood flow but there are other applications in ophthalmology. For example, an initial study has been performed to use the technique to determine the velocity of the contractions of the extraocular muscles during saccades ²⁷. These saccadic velocities were reduced after the injection of

Botulinum toxin into the muscle. Duplex scanning was used by the same investigators for the measurement of the mobility of the vitreous ³⁰⁶.

CDI provides a rapid and convenient method of identification of blood vessels in the eye and orbit. Spectral analysis of the Doppler signals allows the characteristics of the pulsatility of the blood flow in these vessels to be investigated. So far, studies have looked at the blood flow in vascular occlusions and intraocular tumours primarily, as well as describing miscellaneous orbital conditions. Further use of the technique can only be made if certain basic information is obtained such as reproducibility. Currently, interpretation of the results of studies is difficult because basic investigations have not been performed. The next chapter describes studies in this area.

3 Chapter 3

ASSESSMENT OF COLOUR DOPPLER IMAGING IN A NORMAL POPULATION.

3.1 Summary

A control population was examined to determine the blood vessels in the orbit from which measurements of blood velocity could be obtained. Although multiple blood vessels could be imaged only the results from the ophthalmic artery and central retinal artery and vein were reproducible. Normal ranges were defined for these vessels. Age, systolic blood pressure and smoking habit were found to influence the results obtained. The inter-relationship of the velocities showed that there was, in particular, a relationship between the velocities in the central retinal artery and vein.

3.2 Introduction.

The application of any new examination technique requires the investigation of various parameters in a population of normal individuals to allow experience to be gained, normal ranges to be determined and the inherent variability of the technique assessed. This section of the study was performed to investigate the technique of colour Doppler ultrasound imaging as a means of measuring blood velocity in the eye and orbit. The group was examined to identify the blood vessels from which blood velocities could be obtained and the reproducibility of the velocity measurements measured. A group of volunteers was imaged to produce normal ranges for the Doppler results and to identify correlations of the results with age, systemic blood pressure, smoking habit and the presence of systemic vascular diseases. The effect of postural changes was examined and the effect on intraocular pressure from the application of the ultrasound transducer investigated.

3.3 Method of Colour Doppler Imaging.

An Acuson 128 (Mountain View, California) colour Doppler ultrasound imager with a 7.5 MHz linear array surface transducer was used (figure 3.1). The machine is controlled via a computer keyboard with an integral rollerball and real time images displayed on a visual display unit. The machine settings are varied for optimal imaging whilst at the same time restricting the ultrasound energy being applied to the tissue. An "application" setting for "eyes" was used at a stimulus power of -0.09 dB. The ultrasound exposure duration was kept as short as possible, in particular, pulse Doppler imaging was limited to a maximum of 10 secs of continuous duration.

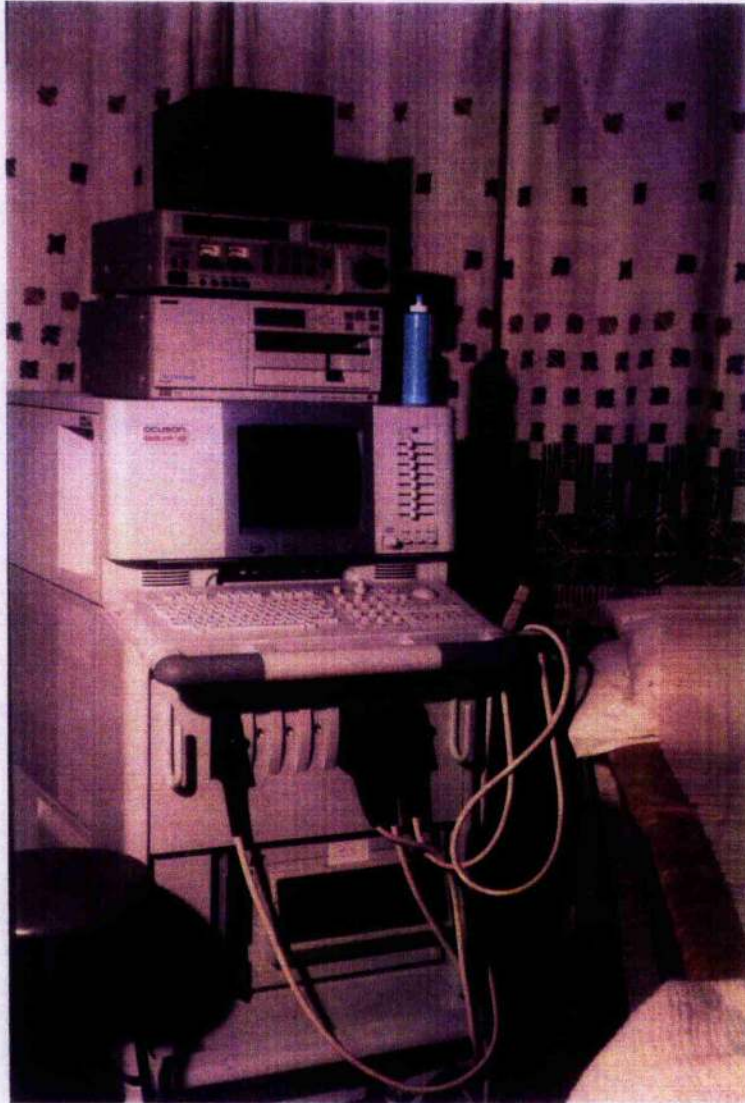


Figure 3.1. The Acuson 128 machinery is shown.

3.3.1 Management of the Patient or Volunteer During CDI.

The patient lay in the supine position for three minutes before commencing scanning. In this way the systemic blood pressure and pulse rate were allowed to reach a resting level. The procedure was explained to the patient and the name and date of birth of the patient and date of examination recorded for identification of the scan during later analysis. The subject was asked to close the eyelids, avoid eye movements and direct their gaze towards the ceiling of the room. The ultrasound transducer was applied with contact jelly to the eyelid whilst the hand of the examiner rested upon the patient's inferior orbital margin thereby minimising the pressure on the globe. The 7.5 MHz transducer was applied in the horizontal axis, therefore all images presented in the figures are in a horizontal transverse plane.

3.3.2 The imaging was performed in four stages:

A. B MODE IMAGING.

B mode ultrasound was used to produce a two dimensional image of the eye and orbit allowing identification of the structures of the region. The vitreous cavity was identified by its hyporeflective (dark) appearance and the orbital fat by its hyperreflective (white) appearance. The curvature of the posterior pole of the eye can therefore be identified where the fat and the vitreous cavity meet. Within the orbital fat the optic nerve was detected as a hyporeflective band extending posteriorly from just nasal to the posterior pole of the eye.

B. COLOUR IMAGING.

After identification of the structures of the eye and orbit the ultrasound setting was changed to provide a colour coded image. During this part of the procedure the ultrasound signal from the transducer was divided into two portions. The first continued to produce a B scan image on the visual display unit (VDU) but at a lower temporal frequency (the image changes less often making "real time" observation of the tissues less sensitive). The second portion of ultrasound signal was employed to detect Doppler frequency shifts which were represented as coloured pixels on the B scan image on the VDU and situated at the appropriate anatomical

location. A blue green red orange yellow scale set to detect Doppler frequency shifts from -0.06 to 0.06 dB was used. With the eye immobile, frequency shifts were produced from the movement (flow) of red blood cells in the blood vessels. In this way the blood vessels could be located and their direction of flow determined, the red spectrum indicating movement towards and blue away from the probe. Changes in the velocity of the flow (pulsation) were detectable because the VDU image was constantly renewed. The vasculature was identifiable by its anatomical location on the B scan according to the anatomical descriptions of Hayreh^{99,103}, by the direction of blood flow and ultimately by the pulsatile flow characteristics in the vessel.

C. OBTAINING A VELOCITY WAVEFORM.

After identification of the vessel of interest by its anatomical location and appearance on the scan, a cursor on the VDU (controlled by the rollerball on the keyboard) was used to aim a pulsed Doppler ultrasound beam at the vessel. Higher intensity ultrasound with a sample gate of 1.5mm x 1.5mm, was employed. The ultrasound frequency shifts were converted by computerised mathematical analysis using Fast Fourier Transformation into a spectral waveform of the blood velocities against time. If the direction of the blood flow was visible on the colour image, the conversion of

the frequency shifts into velocity values (cm/s) was adjusted for the angle of incidence of the Doppler beam to the direction of flow (angle correction). The pulse waveforms showed a spectrum of blood cell velocities which were displayed on a graph of velocity against time. Velocity towards the probe was shown above the x axis and away from the probe below the x axis. The upper border (or lower border for flow away from the probe) of the waveform represented the maximum velocity recordable in the vessel at that time (peak velocity). The area beneath the curve represented the other velocities from slower moving blood cells. An illustration of a common carotid waveform is shown in figure 3.2 and illustrates the typical features of spectral analysis of arterial blood velocities.

D. BLOOD VELOCITY MEASUREMENT.

Once a series of waveforms was obtained these were "frozen" on the VDU and recorded on VHS magnetic videotape. Velocities were measured by directing a cursor on the screen (using the rollerball) to the appropriate part of the waveform. In order to minimise the effect of respiratory function on the velocities three consecutive pulse waveforms were measured, ie., over the duration of one respiration at 20 breaths per minute. If three consecutive pulses were unobtainable the blood vessel was categorised as unrecordable.

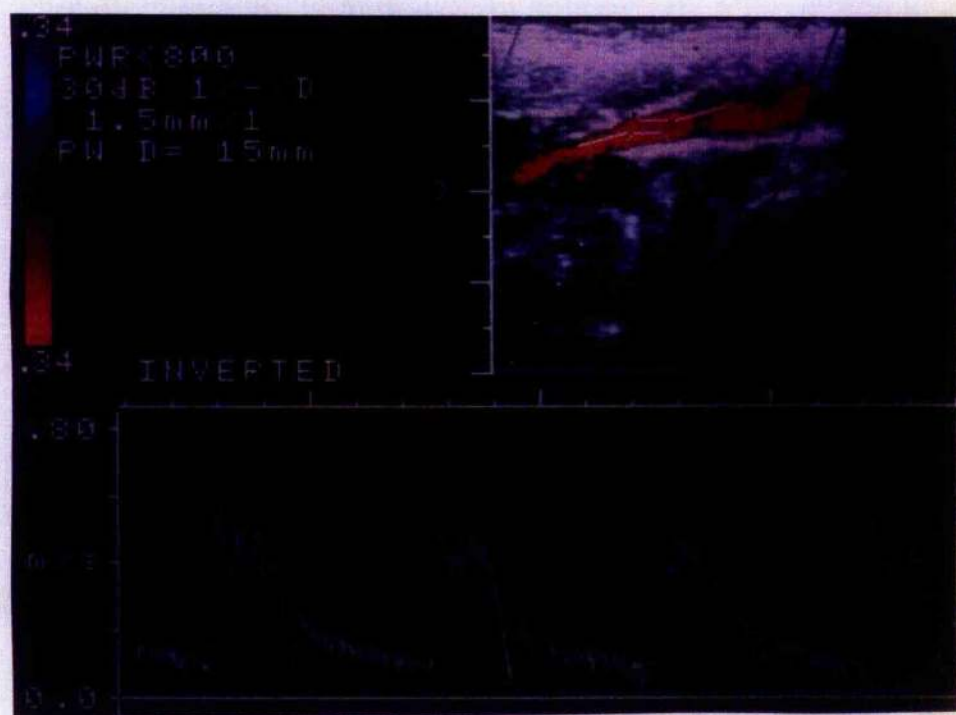


Figure 3.2. A colour Doppler image of the blood velocities in the carotid circulations and the spectral waveform obtained from the common carotid.

Three arterial measurements were taken:

Peak Systolic Velocity (PSV) - The maximum velocity in the blood vessel in the systolic phase of the blood flow.

End Diastolic Velocity (EDV) - The maximum velocity at the end of the diastolic phase of the blood flow.

Resistive index - Calculated from the formula:

$$\text{Resistive index} = \frac{\text{PSV} - \text{EDV}}{\text{PSV}}$$

This ratio is an indicator of the shape of the frequency time display waveform and can be used to avoid the error that the angle of travel of blood flow might induce upon absolute measurements of velocity. An increase in the resistance to flow distal to the site of measurement causes an increase in the resistive index, whereas, a constriction of the vessel proximal to the site of measurement decreases the index.

Three venous measurements were obtained:

Maximum Peak Velocity (Vmax) - The maximum velocity during one cardiac cycle.

Minimum Peak Velocity (Vmin) - The minimum peak velocity during one cardiac cycle.

Venous Pulsatility Index (VPI) - Calculated from the formula:

$$\text{Venous Pulsatility Index} = \frac{V_{\text{max}} - V_{\text{min}}}{V_{\text{max}}}$$

The nomenclature "Vmax" and "Vmin" were employed for the venous velocities because these peak velocities did not necessarily occur during the systolic or diastolic phases of the arterial cycle. Similarly, although the resistive index formula (which was described by Pourcelot ²¹⁷ for arterial Doppler recordings) was used for the venous waveforms as a measure of the "pulsation" of blood flow in the vein, the nomenclature "venous pulsatility index" was employed.

3.3.3 SELECTION OF THE CONTROL POPULATION.

Ninety five volunteers were examined to provide control data and consisted of staff of the Ophthalmology or Radiology department at the Western Infirmary Hospital, Glasgow and relatives of the patients attending the central retinal vein occlusion study or the ophthalmology out patient department. The volunteers were asked for a history of general medical and ocular conditions, drug usage and smoking habit. Subjects with a history of previous ophthalmological disorders were excluded. Systemic blood pressure was measured using a digital sphygmomanometer and intraocular pressure was recorded with a Goldman or Perkins applanation tonometer. One orbit only of each volunteer was examined (right or left eyes were chosen by random number sequences).

DATA STORAGE AND ANALYSIS.

All data were stored on specially designed databases using FoxPro II software and analysed using CSS Statistica software on an IBM compatible personal computer. Graphs were produced using CSS Statistica or Harvard Graphics.

3.3.4 REPRODUCIBILITY OF COLOUR DOPPLER IMAGING.

In fifteen healthy volunteers attempts were made to detect and record blood velocities from the following vessels in the orbit:

- Ophthalmic Artery
- Central Retinal Artery
- Central Retinal Vein
- Temporal Posterior Ciliary Arteries
- Nasal Posterior Ciliary Arteries
- Temporal Vortex Vein
- Nasal Vortex Vein
- Superior Ophthalmic Vein.

Spectral analysis of the vessels was obtained on two occasions by one observer to allow the assessment of intraobserver reproducibility. In addition, the ophthalmic artery, central retinal artery and vein were examined by another observer, allowing the investigation of interobserver reproducibility. This observer was masked from the results obtained by the previous observer. This part of the study required repeated ultrasound examinations over a period of 1 hour. To restrict the dosage of ultrasound energy being applied to the tissue for reasons of safety, the posterior ciliary arteries, superior ophthalmic vein and vortex veins were not examined in the interobserver comparison. Systemic blood pressure and pulse were recorded before each examination by digital sphygmomanometer.

The order of the examinations was randomly varied. Each observer measured mean PSV, EDV and resistive index from three consecutive waveforms from the arteries and Vmax, Vmin and venous pulsatility index from the veins.

3.3.5 STATISTICAL ANALYSIS AND INTERPRETATION OF THE RESULTS.

The results were statistically analysed by obtaining the mean difference between the Doppler results obtained during the intraobserver and interobserver examinations. These were presented as the mean difference and the standard deviation of the mean difference (SD) ¹⁹. The mean difference provides a measure of whether there is a consistent error in the results obtained between two examinations. If the value was negative the second examination has provided lower results and if positive higher results have been obtained. Doubling the SD of the mean difference has been used as a measure of the inherent variability between the examinations, eg., a SD of the mean difference of 10 for results with mean value of 100 would indicate a variation of 20%. The least variation is present when the mean difference and the SD both equal zero. Systemic blood pressure and pulse were similarly assessed to determine any difference in these

systemic parameters during the examinations.

3.3.6 PRODUCTION OF NORMAL RANGES

Normal ranges were calculated by adding and subtracting 2 SD from the mean values for the Doppler results of the ophthalmic artery and central retinal artery and vein (the upper and lower confidence limits were also given for comparison with subsequent means from populations of patients with ocular disease). Fifteen volunteers with a past history of systemic disease such as hypertension, maturity onset diabetes or arteriopathy were excluded from the data for the production of these normal ranges. In twenty individuals the blood velocities in the ophthalmic artery were measured at the orbital apex and in the nasal orbit to determine any difference in the results from these two sites. In the remainder of the control population the ophthalmic artery was examined only in the nasal orbit.

3.3.7 CORRELATIONS WITH OTHER FACTORS.

The influence of age, right or left eye, sex, systolic and diastolic blood pressure, cigarette smoking and the presence of vascular disease were examined by Spearman rank correlation, multiple linear regression analysis or analysis of covariance where appropriate. R and p values for rank correlation and p values for analysis of covariance are shown. For multiple linear

regression results were described as significant at p less than 0.05.

The difference between the Doppler results from the three vessels was determined using Wilcoxon matched pairs testing. Secondly, the relationship of the velocity values to each other was examined by observing scattergrams and employing Spearman rank correlation.

3.3.8 THE LEARNING CURVE.

Since the cases were numbered sequentially with those examined early in the course of the study given low case numbers it was possible to gain an idea of the learning curve for the technique from the scatter of the Doppler values against the case number of the volunteer.

3.3.9 DETERMINATION OF THE EFFECTS OF POSTURE ON THE ARTERIAL BLOOD VELOCITIES.

INTRODUCTION.

Postural changes are known to occur in the blood flow to the eye in the choroid whereas autoregulation maintains a steady flow in the retina. For this reason, it was important to determine whether postural changes would alter the velocity results and decide upon a position in which future scans would be performed. The results could also provide a way of assessing the autoregulatory capacity of the vasculature for its use in future studies of diseases in which this may be lost, eg., diabetic retinopathy.

SUBJECTS AND METHOD.

Twenty of the volunteers, 12 males, 8 females, age range 20 to 60 years (mean 34.6), were examined in three postural positions. Initially, each subject was asked to lie supine for five minutes. The systemic blood pressure and pulse rate were then noted. Blood velocities were recorded from the ophthalmic artery and the central retinal artery at the optic nerve either from the left or right eye, according to a predetermined random number sequence. Each subject was then asked to sit upright and all recordings were repeated two minutes later. The subject was asked to stand for two minutes, and all recordings were repeated once

more.

3.4 RESULTS

3.4.1 THE CONTROL POPULATION.

Ninety three volunteers were examined mean age 47.0 years (SD 1.82, range 20-83 years), 56 males and 37 females. Doppler values for all of the volunteers are shown in table 3.1.

THE IDENTIFICATION OF ORBITAL BLOOD VESSELS.

It was found that the Bscan image of the optic nerve provided the most useful landmark for the identification of the anatomical location of the blood vessels for a number of reasons. The blood vessels listed below were identifiable and provided velocity recordings:

- The ophthalmic artery was situated either above or below the optic nerve in the posterior orbit before passing forward in the nasal orbit in a horizontal plane slightly superior to that of the optic nerve, (figure 3.3). The velocity waveform from the artery possessed a profile similar to the internal carotid with a high PSV spike followed by a rapid drop in the velocity to a low EDV. A dichrotic notch from the closure of the aortic valve was usually present and a window indicating relatively uniform blood flow occasionally seen (figure 3.4). The results of blood

Table 3.1
The results from 95 volunteers.

	n	Range	mean	SD	Confidence limits	
					upper	lower
AGE	95	20-83	47	1.82		
Ophthalmic Artery						
PSV	95	11.0-65.0	35.0	11.2	37.3	33.5
EDV		1.9-23.0	8.6	3.8	9.4	7.8
RI		55.7-89.7	74.0	8.2	75.8	72.4
Central Retinal Artery						
PSV	95	4.6-18.6	10.2	2.8	10.8	9.6
EDV		1.3-6.3	3.1	1.1	3.3	2.8
RI		56.0-89.0	69.3	7.7	70.9	67.7
Central Retinal Vein						
Vmax	76	3.0-11.0	5.7	1.4	6.1	5.4
Vmin		2.0-7.7	3.8	0.8	4.0	3.6
RI		13.5-60.0	32.4	9.7	34.6	30.1

Table 3.1. The means (SD), confidence limits and range of values are shown for the ophthalmologically healthy volunteers for the ophthalmic artery and central retinal artery and vein.



Figure 3.3. A normal color Doppler image of the left orbit showing the blood flow in the ophthalmic artery indicated by the coloured pixels (arrow).

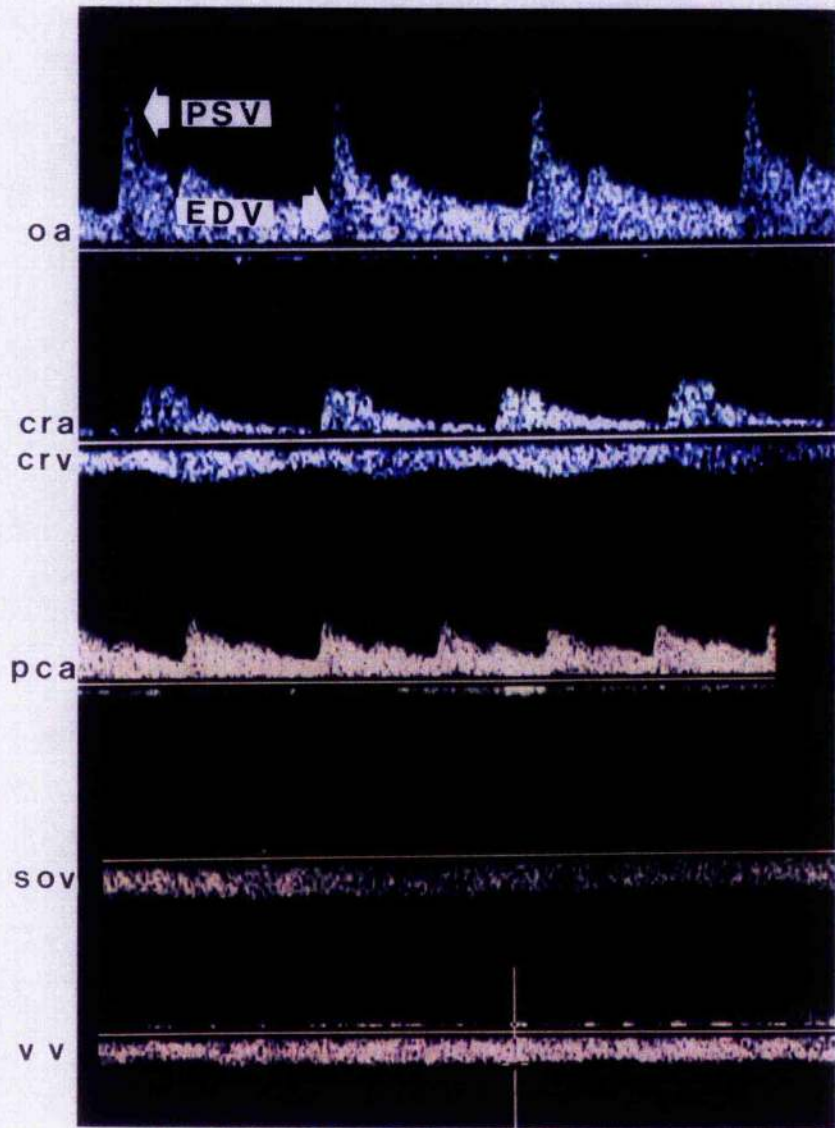


Figure 3.4. The blood velocity waveforms produced by spectral analysis of Doppler signals from the eye and orbit of a young healthy subject showing from top to bottom the ophthalmic artery (OA), the central retinal artery (CRA) and vein (CRV), a posterior ciliary artery (PCA) and the superior ophthalmic vein (SOV) and a vortex vein (VV). The arrows indicate the portions of the waveform which correspond to peak systolic velocity (PSV) and end diastolic velocity (EDV) in the ophthalmic artery.

velocity measurements from the ophthalmic artery at the orbital apex and the nasal orbit were similar.

- The central retinal artery and vein were detected within the optic nerve in its retrolaminar portion for a length of approximately 10mm. They were adjacent to each other (figure 3.5) and were seen as a blue and red band of coloured pixels on the VDU within the optic nerve at an average of 15.1° to the anteroposterior meridian. The central retinal arteries provided a velocity profile which was relatively smoothed out in comparison to the ophthalmic artery and the posterior ciliary arteries (figure 3.4).

- The posterior ciliary arteries commenced as trunks approximately 10-20mm behind the globe before forming multiple branches surrounding the optic nerve in its retrobulbar portion. The waveform produced in these vessels provided velocity values which were similar to the central retinal artery but with a sharper PSV spike (figure 3.4). These vessels were examined on the nasal and temporal sides of the nerve (figure 3.5).

- The superior ophthalmic vein (usually a larger sized vessel than the other veins) took an oblique course superior to the optic nerve in the centre of the retrobulbar orbit (figure 3.6). The flow pattern in this vessel and direction of flow was variable, sometimes the flow was constant or phasic with the respiration of the individual (figure 3.4) and in one case demonstrated a flow pattern similar to that of the

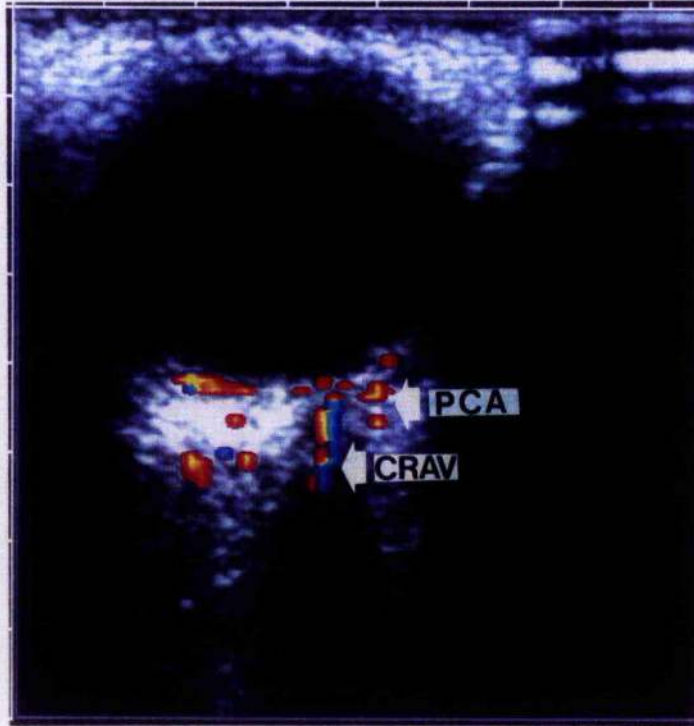


Figure 3.5. A normal color Doppler image of the right orbit showing the blood flow in the central retinal artery and vein (CRAV) and the posterior ciliary arteries (PCA).

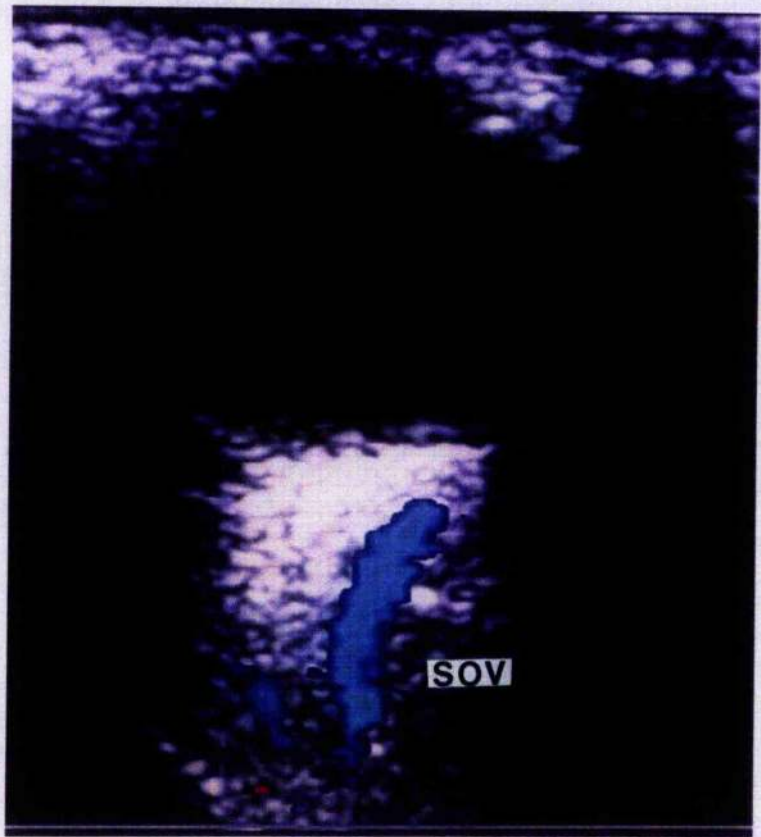


Figure 3.6. The superior ophthalmic vein (SOV) is shown in the superior orbit above the optic nerve. The direction of flow in this vessel may be anteriorly or posteriorly in normal individuals.

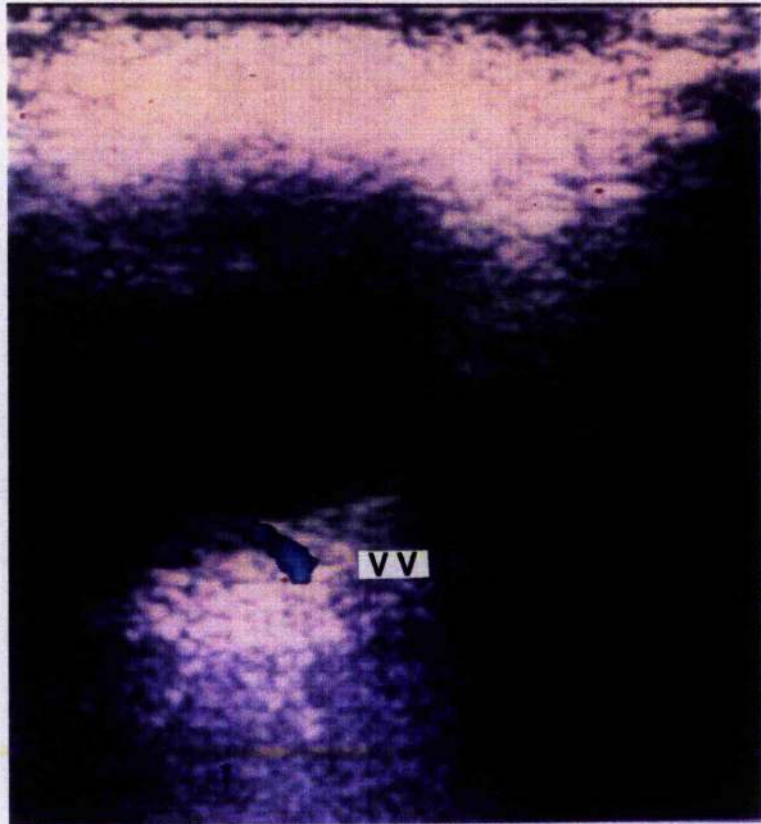


Figure 3.7. The color Doppler image of a vortex vein (VV) as it exits the globe of the eye. These vessels provide variable results and may be difficult to detect in normal individuals.

jugular vein.

- The vortex veins were located in a horizontal plane either above or below that of the optic nerve as they exited the sclera just posterior to the equator of the eye (figure 3.7) and demonstrated flow of a constant velocity (figure 3.4).

3.4.2 REPRODUCIBILITY

INTRODUCTION.

Fifteen volunteers were examined by colour Doppler imaging to inspect the reproducibility of the method for two examinations by the same ultrasonographer (examinations 1 and 2 intraobserver variability) and between examinations by two ultrasonographers (examinations 1 and 3, interobserver variability). Systemic blood pressure and pulse were monitored throughout.

SYSTEMIC BLOOD PRESSURE AND PULSE RATE.

Systolic and diastolic blood pressures and pulse rate were similar between examinations 1 and 2, but the diastolic blood pressure was significantly lower between observations 2 and 3 (paired t test $p=0.01$, table 3.2). Analysis showed that as the disparity between the diastolic blood pressure in observations 2

Table 3.2

	1	2 (Mean and SD)	3
SBP (mmHg)	122 (12)	121 (20)	122 (11)
DBP (mmHg)	73 (8)	69 (8)	77 (7)
Pulse (/min)	68 (12)	69 (13)	71 (15)

Table 3.2. Systemic pulse and blood pressures in the reproducibility analysis showing a rise in diastolic blood pressure in the interobserver examination, 1 and 3 (DBP = diastolic blood pressure, SBP = systolic blood pressure).

and 3 increased, the disparity between the resistive indices in the ophthalmic artery also increased (Spearman Rank correlation, $r = 0.49$, $p = 0.03$). All other comparisons of the difference in blood pressure or pulse and velocimetry did not show any correlation. In one individual a large variation in systolic blood pressure from 132 mmHg to 172 mmHg was associated with a rise in the central retinal artery PSV of 3.3 cm/sec and EDV of 2.0 cm/sec and a rise in the nasal posterior ciliary artery PSV of 8.4 cm/sec and EDV of 12.7 cm/sec in the intraobserver comparison and the results from this individual were removed from the analysis. In addition, during the interobserver comparison the velocity results from one individual were particularly dissimilar from the rest of the group and were therefore removed.

ORBITAL ARTERIES.

Reproducibility of the Doppler results from the orbital arteries are shown as the mean difference in the values between examinations and its standard deviation, table 3.3. The measurements from the ophthalmic artery and central retinal artery between observations were similar.

Notably, the mean differences in the results from the posterior ciliary arteries (intraobserver analysis only) are higher and more variable, and the relatively larger standard deviations of these means indicate that

Table 3.3

(n)	mean velocity cm/sec		mean differences cm/sec		t Tests	
	(SD)		(SD)			
	1+2	1+3	1-2	1-3	1-2	1-3
Ophthalmic Artery						
PSV	39.7	39.2	0.5	2.6	ns	ns
14	7.3	7.8	2.1	3.2		
EDV	10.9	10.2	0.7	0.5	ns	ns
14	3.2	3.0	1.2	2.6		
RI	72.7	74.0	-0.3	-1.6	ns	ns
14	5.0	4.8	3.5	4.6		
Central Retinal Artery						
PSV	11.5	10.9	0.4	0.8	ns	ns
14	2.0	1.9	1.4	2.1		
EDV	4.0	3.6	0.2	0.8	ns	ns
14	1.0	0.9	0.8	0.9		
RI	65.6	67.1	-0.4	-3.4	ns	ns
14	6.4	5.7	4.2	4.2		
Nasal Posterior Ciliary Artery						
PSV	12.1		0.9		ns	
14	3.3		3.6			
EDV	5.4		-1.1		ns	
14	2.5		1.2			
RI	60.4		1.0		ns	
14	7.0		8.2			
Temporal Posterior Ciliary Artery						
PSV	12.3		0.1		ns	
14	4.2		4.5			
EDV	4.9		-0.1		ns	
14	2.0		1.9			
RI	60.0		6.8		ns	
14	6.4		6.0		ns	

Table 3.3 The intraobserver (comparisons between 1 and 2) and interobserver (comparisons between 1 and 3, and 2 and 3) reproducibility for velocimetry results from the orbital arteries. It is notable that the mean difference in the posterior ciliary results are more variable, and the relatively larger SDs of these means indicate a greater variation between two examinations than for the ophthalmic artery and central retinal artery.

a greater variation exists between any two examinations than for the ophthalmic artery and central retinal artery. The resistive indices showed less variation than the velocity measurements but were still higher than in the other arteries.

ORBITAL VEINS.

The results of reproducibility of the orbital veins are shown on table 3.4. The mean differences between measurements from the central retinal vein are much smaller than the other veins and comparable to the results from the ophthalmic and central retinal arteries. The superior ophthalmic vein and the vortex veins often showed significant differences between the results from the examinations. In addition, these veins were undetectable in many of the orbits examined, eg., the superior ophthalmic vein was undetectable in either of the examinations in two cases, in the nasal vortex vein in 6 cases and in the temporal vortex vein in 5 cases. In 2 further patients the nasal vortex veins were only detectable in one of the observations and in 3 of the patients the temporal vortex veins were only detectable once.

The coefficients of variation of repeated measures are shown for the results of the study of reproducibility of colour Doppler recordings (figure 3.8). Coefficients of variation were higher for the results of PSV

Table 3.4

mean velocity		mean differences		t Tests	
(n)	cm/sec		cm/sec		
	(SD)		(SD)		
	1+2	1+3	1-2	1-3	1-2 1-3
Central Retinal Vein					
Vmax	5.9	5.9	0.1	0.3	ns ns
14	1.2	1.3	0.8	1.2	
Vmin	4.1	4.1	-0.2	0.0	ns ns
14	0.8	0.9	0.5	0.9	
VPI	29.9	30.0	1.0	-0.1	ns ns
14	5.4	8.2	2.7	6.8	
Superior Ophthalmic Vein					
Vmax	9.5 (4.0-15)				
12	3.4				
Nasal Vortex Vein					
Vmax	13.4 (8-21)				
8	5.0				
Temporal Vortex Vein					
Vmax	8.4 (5-10)				
7	2.1				

Table 3.4. The intraobserver (comparisons between 1 and 2) and interobserver (comparisons between 1 and 3, and 2 and 3) reproducibility for the orbital veins. The mean differences (and SDs) of measurements from the central retinal vein are small indicating good reproducibility. There are significant differences in the mean intraobserver measurements of the superior ophthalmic vein and the vortex veins. In addition, out of the 14 orbits examined, blood flow was undetectable on both occasions in the superior ophthalmic vein in 2 cases, in the nasal vortex vein in 6 cases and in the temporal vortex vein in 5 cases. In 5 cases the vortex veins were detectable on one examination only.

Acuson 128 Reproducibility

Coefficient of Variance of Repeated Measures (%)

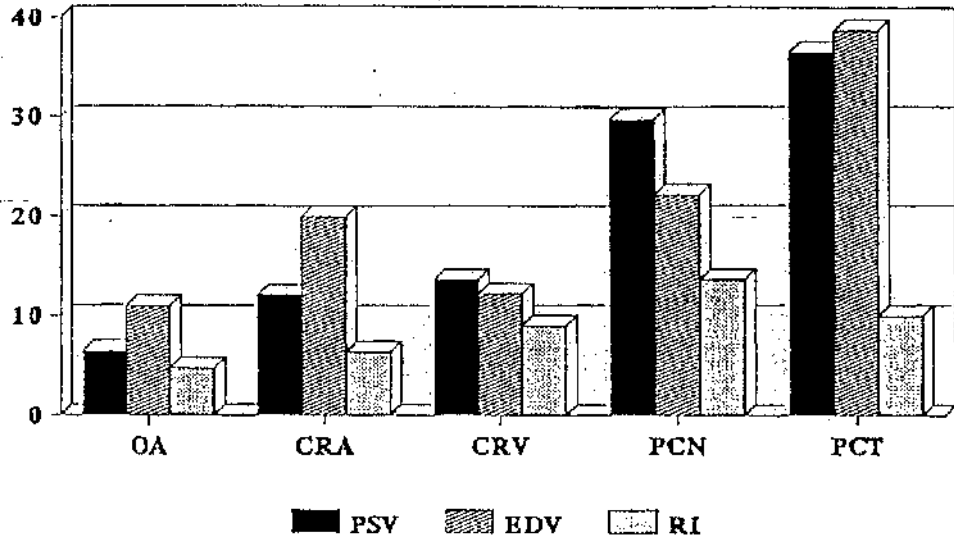


Figure 3.8. The coefficients of variation of repeated measures are shown for the various measurements and blood vessels in the intracobserver comparison.

Ophthalmic artery (OA)
 Central retinal artery (CRA)
 Central retinal vein (CRV)
 Nasal posterior ciliary arteries (PCN)
 Temporal posterior ciliary arteries (PCT)
 Peak systolic velocity (PSV)
 End diastolic velocity (EDV)
 Resistive index (RI).

and EDV than for resistive index. The coefficients of variation are much higher from the posterior ciliary arteries than the ophthalmic artery, central retinal artery and vein.

3.4.3 NORMAL RANGES.

The normal ranges are shown in table 3.5. Age adjusted normal ranges did not influence these results appreciably. Only values for the venous pulsatility index in the central retinal vein (which demonstrated the largest r value by Spearman rank correlation for age, $r=0.49$) produced normal ranges which were notably different, ie., 13.5% to 41.5% for those less than 50 years and 16.6% to 55.0% for patients of 50 years of age or more.

3.4.4 INFLUENCE OF SYSTEMIC PARAMETERS.

These effects are summarised on table 3.6.

AGE

Ophthalmic artery velocities showed a negative correlation age (both PSV and EDV, $r=-0.31$, $p=0.003$, figure 3.9). Resistive index in the central retinal artery and pulsatility index in the vein showed a positive correlation ($r=0.21$, $p=0.04$ and $r=0.54$, $p<0.00001$, figure 3.10).

Multiple regression analysis (including the variables

Table 3.5
Normal Ranges

	Normal Range (Age 20-83 years) (cm/sec)	Upper and Lower Confidence Limits of the Mean ($p=0.95$) (cm/sec)
Ophthalmic Artery		
PSV	12.4-58.1	33.0-38.1
EDV	1.1-17.8	8.0-9.8
RI	56.8-90.4	71.8-75.5
Central Retinal Artery		
PSV	5.0-15.4	9.6-10.8
EDV	1.1-5.1	2.9-3.4
RI	53.5-83.9	67.0-70.4
Central Retinal Vein		
Vmax	2.7-8.7	6.1-5.3
Vmin	2.2-5.6	3.7-4.1
VPI	12.8-48.8	28.4-33.1

Table 3.5. The normal ranges and confidence limits of blood velocities are provided for the ophthalmic artery and the central retinal artery and vein for 80 systemically and ophthalmologically healthy volunteers.

Table 3.6
The Variation of Velocity Measurements with Systemic
Features.

	Age	SBP	DBP	Smoking
Age		+	+	+
Ophthalmic Artery				
PSV	-	+		-
EDV	-			
RI	-			-
Central Retinal Artery				
PSV		+		
EDV				
RI	+			
Central Retinal Vein				
Vmax				
Vmin				
VPI	+			

Table 3.6. The effects of the various systemic parameters are shown with + and - indicating a positive or negative correlation respectively.

Ophthalmic Artery Velocity v Age

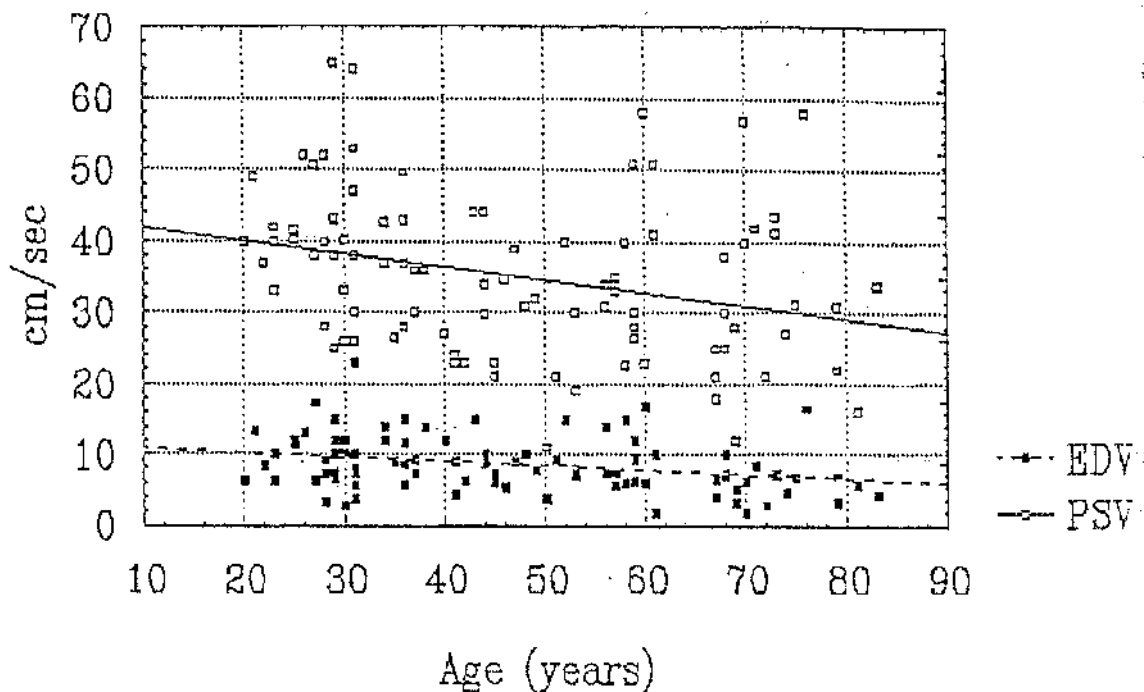


Figure 3.9 The blood velocities in the ophthalmic artery (peak systolic blood velocity, PSV, and end diastolic blood velocity, EDV) had a negative correlation with age ($r=-0.31$, linear regression lines are shown).

Retinal Vessels v Age

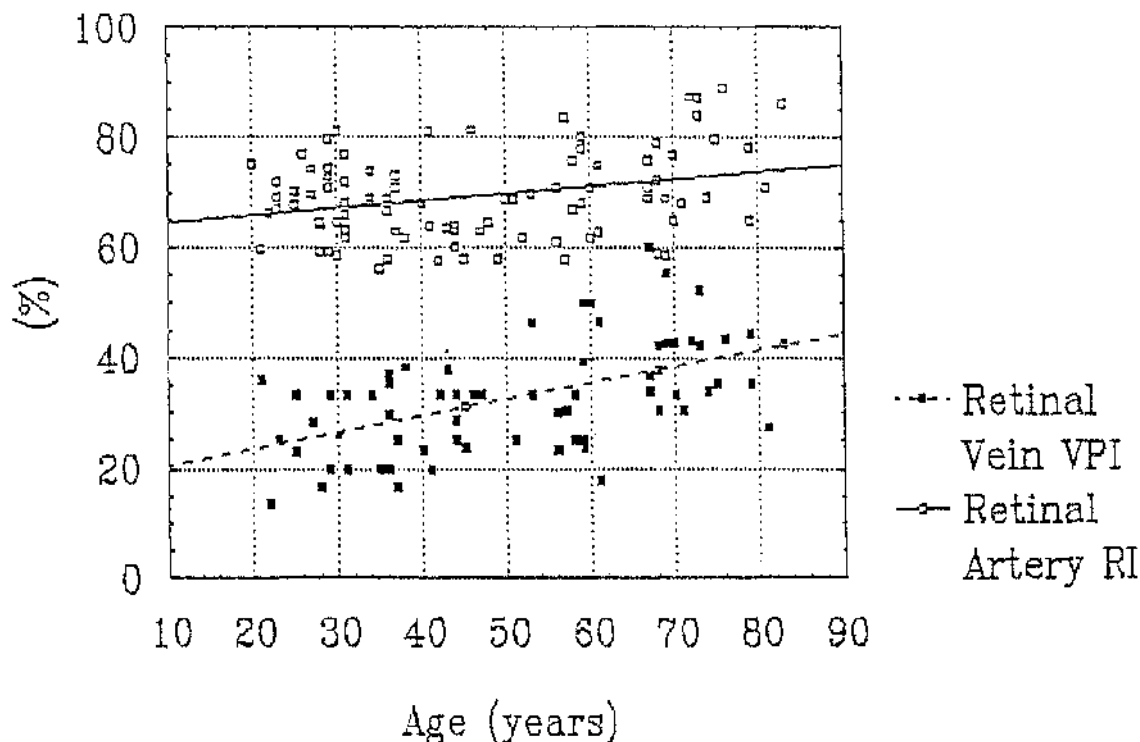


Figure 3.10. The resistive index in the central retinal artery and venous pulsatility index in the vein demonstrated a positive correlation with age ($r=0.21$ and $r=0.34$ respectively, linear regression lines are shown).

systemic blood pressure and smoking habit) confirmed the negative correlation of age with the velocities in the ophthalmic artery and the positive correlation with the resistive index in the central retinal artery and pulsatility index in the vein.

SEX

There were no differences found for the velocity results for males or females (multiple linear regression including age, systemic blood pressure and smoking habit).

SYSTEMIC BLOOD PRESSURE.

Systolic and diastolic blood pressure increased with age (both $r=0.49$ and $p<0.0001$). Multiple linear regression analysis (age, blood pressure, smoking habit) showed that the PSV in both of the arteries was positively correlated with systolic blood pressure (ophthalmic artery $b=0.56$ and central retinal artery $b=0.39$, figure 3.11). No change was found for diastolic blood pressure.

CIGARETTE SMOKING HABITS.

A history of smoking habit was elicited from ninety individuals, of these two pipe or cigar smokers were excluded leaving 19 smokers, 60 non smokers and 9 exsmokers for comparison by ANCOVA with the covariants

PSV in the Arteries

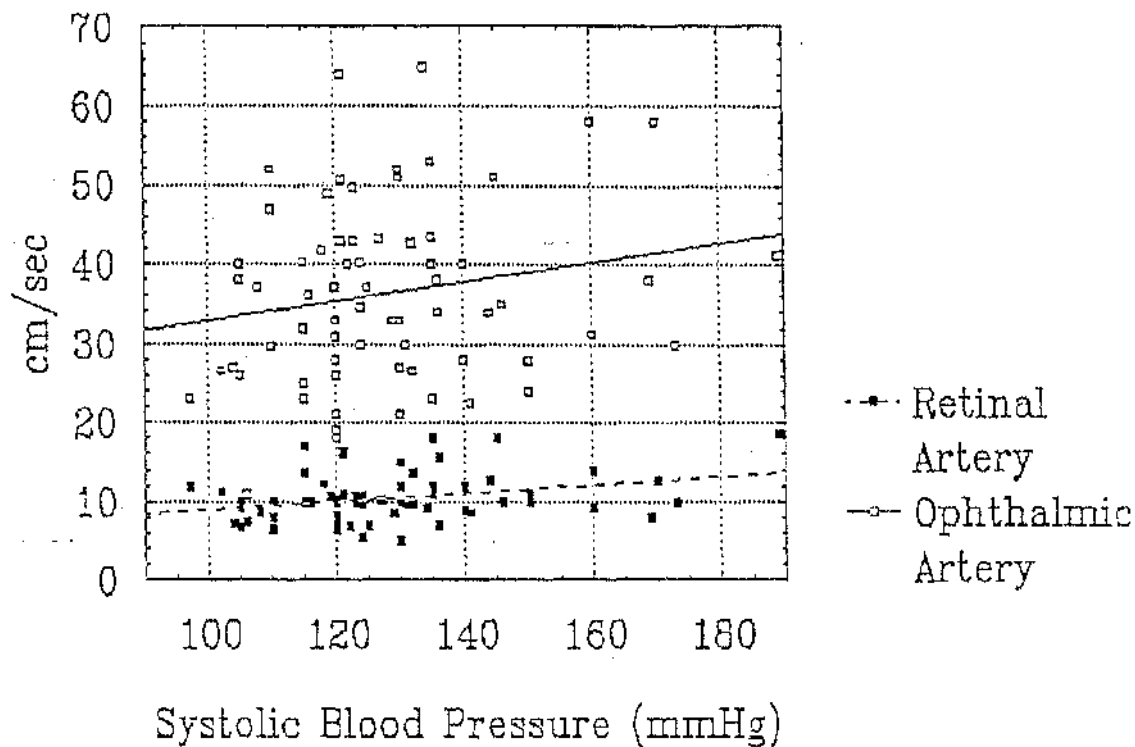


Figure 3.11. The effect of raised systemic blood pressure on the peak systolic blood velocities (PSVs) in the ophthalmic and central retinal artery are indicated demonstrating negative correlations ($r=0.56$ and $r=0.39$ respectively, linear regression lines are shown).

Smoking v Ophthalmic Artery Velocity

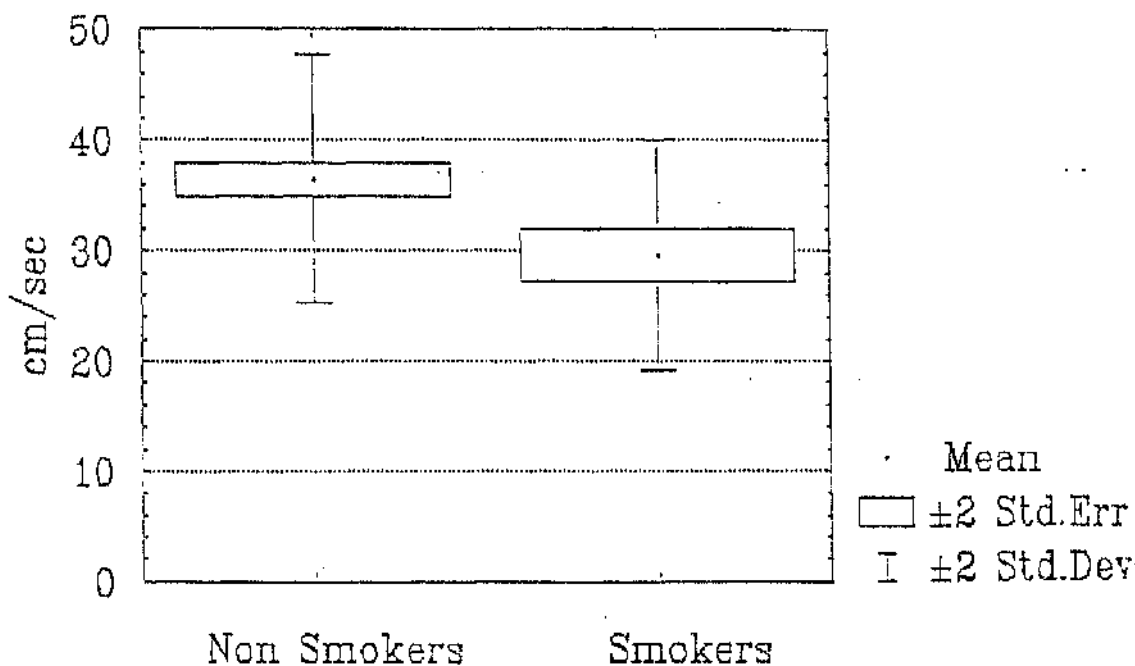


Figure 3.12. The values for mean peak systolic velocity (SE and SD) in the ophthalmic artery of smokers and non smokers are illustrated. A reduction in the peak systolic velocity can be seen in those volunteers who smoke.

age and systemic blood pressure. Mean ophthalmic artery PSV was lower in smokers 29.5 cm/s (SD 10.4) than non smokers 36.5 cm/sec (SD 11.2, $p=0.03$, figure 3.12) and therefore the resistive index in the ophthalmic artery was also lower in the smokers 69.7% (SD 6.0) than nonsmokers 75.6% (SD 8.4, $p=0.003$). Ex smokers had similar results to the nonsmokers for example in the ophthalmic artery a mean PSV of 36.9 cm/sec (SD 13.0) and a mean resistive index of 72.1% (SD 7.1). The other Doppler measurements demonstrated no differences after statistical analysis.

ARTERIOPATHY AND HYPERTENSION.

There was no difference in the Doppler measurements from healthy individuals and a small group of 5 elderly patients with a history of arteriopathic disease (myocardial infarction, angina or cerebrovascular accident) or with a group of 8 patients on observation or treatment for hypertension. Two patients suffered from maturity onset diabetes with no retinopathy, one diet controlled the other on oral hypoglycaemics.

NB: Any comparisons with the patients with central retinal vein occlusion include the whole group of volunteers because of the high incidence of systemic disease in these patients.

RIGHT OR LEFT EYES.

No significant differences were found in the Doppler results from right or left eyes.

3.4.5 THE INTER-RELATIONSHIP OF THE VELOCITY MEASUREMENTS.

The Doppler measurements were compared with each other to determine whether there was any relationship between the flow in the ophthalmic artery, central retinal artery and vein. First of all the differences between the blood velocities in the three vessels were determined by Wilcoxon matched pairs test.

Not surprisingly PSV in the ophthalmic artery was significantly higher than in the central retinal artery which was significantly higher than the Vmax in the central retinal vein (all $p < 0.0001$). Although the ophthalmic artery had a significantly higher EDV than the artery and the Vmin of the vein, Vmin in the vein was higher than EDV in the central retinal artery. The resistive indices were higher in the ophthalmic artery than in the central retinal artery ($p < 0.0001$).

Secondly the relationship of the Doppler results were defined by use of Spearman Rank correlation.

PSV and EDV or Vmax and Vmin in the same vessel were positively correlated (ophthalmic artery $r = 0.55$, central retinal artery $r = 0.65$, central retinal vein $r = 0.81$, all $p < 0.0001$). Ophthalmic artery PSV showed no

correlation with the velocities in the central retinal artery or vein but as the EDV in the ophthalmic artery increased so did the velocities in the central retinal artery ($r=0.24$, $p=0.03$ and $r=0.33$, $p=0.004$).

Velocities in the central retinal vein positively correlated with the velocities in the artery (table 3.7). Also the venous pulsatility index positively correlated with the resistive index in the artery.

Central retinal artery EDV ($r=-0.31$, $p=0.005$) negatively correlated with the resistive index in the ophthalmic artery. Resistive index in the central retinal artery and ophthalmic artery were positively correlated ($r=0.31$, $p=0.006$).

The formula for the calculation of resistive index and venous pulsatility index can be written as:

$$\text{Resistive Index (\%)} = 100 \times (1 - (\text{EDV/PSV}))$$

$$\text{Venous Pulsatility Index (\%)} = 100 \times (1 - (\text{Vmin/Vmax}))$$

Therefore the indices are increased by an increase in PSV or Vmax or a decrease in EDV or Vmin. The results were therefore examined to determine which velocities appeared to influence the resistive indices most. In the ophthalmic and retinal arteries resistive index negatively correlated with EDV ($r= -0.51$, $p=0.000002$ and $r=-0.61$, $p<0.000001$ respectively) whereas the venous pulsatility index positively correlated with Vmax ($r=0.47$, $p=0.0002$).

Table 3.7

Interrelationship of the Velocity Measurements in the Central Retinal Vein and Artery.

	Central Retinal Artery		RI
	PSV	EDV	
	(r and p values)		
Central Retinal Vein			
Vmax	0.33 (0.01)	ns	ns
Vmin	0.28 (0.04)	0.29 (0.03)	ns
VPI	ns	ns	0.34 (0.008)

Table 3.7. The r values (and p) for Spearman rank correlation are provided for the measurements from the central retinal artery and vein in the control population. The venous velocities increase with the arterial velocities and as the pulsation increases in the artery (resistive index, RI) the pulsation also increases in the vein (venous pulsatility index, VPI).

3.4.6 THE LEARNING CURVE.

The scatter of points on scattergrams did not correlate with case number. In addition, multiple linear regression analysis including the variables age, smoking habit and systemic blood pressure showed that there was no correlation of the Doppler measurements with the case number.

3.4.7 THE DETERMINATION OF THE EFFECTS OF POSTURE ON THE BLOOD VELOCITIES.

No effect of a change in posture was seen in velocimetry readings at any of the sites measured despite rises in diastolic blood pressure and pulse when changing from a supine or sitting position to standing (table 3.8, rises in diastolic blood pressure and pulse rate were significant at $p < 0.01$ and $p < 0.05$ respectively). There was however a trend for a reduction in ophthalmic artery blood velocities.

Table 3.8

	Pulse (beats/min)	SBP (mmHg)	DBP (mmHg)	PSV (ms^{-1})	EDV (%)	RI
Supine	70.6	118.0	71.7	33.7	7.5	77.3
Sitting	72.6	113.5	72.9	30.0	5.7	81.6
Standing	78.6*	114.0	79.8#	27.3	5.5	79.8

Table 3.8. The results of changes in posture are shown for mean pulse rate, systemic systolic (SBP) and diastolic blood pressure (DBP) with a significant rise in both DBP and pulse rate (* $p < 0.05$ and # $p < 0.01$). Also shown are the results of blood velocities and resistive indices in the ophthalmic artery of 20 volunteers showing a trend for a reduction in the velocities which was not significant.

3.5 DISCUSSION

There is a need for a technique for the measurement of blood flow in the orbit and eye which can be performed easily and reliably and which can be used to investigate the multiple vascular disorders of this region. In this context colour Doppler imaging was assessed in a control population. It was apparent that multiple blood vessels could be detected in the orbit and spectral waveforms of their velocities obtained. In fifteen volunteers an attempt was made to examine all of the major blood vessels in the orbit to determine the reproducibility of the results. The following blood vessels were detectable and provided velocity measurements:

Ophthalmic Artery

Central Retinal Artery

Central Retinal Vein

Posterior Ciliary Arteries, Nasal and Temporal

Superior Ophthalmic Vein

Vortex Veins, Nasal and Temporal

Only the ophthalmic artery and the central retinal artery and vein produced results which were reproducible. The posterior ciliary arteries provided wide variations up to 75% in velocity values, although with the calculation of resistive index this variation reduced to 20%. The superior ophthalmic vein and vortex veins were undetectable in some individuals. The velocity results obtained from the ophthalmic

artery and central retinal artery and vein were considered reproducible and therefore were recorded in the remainder of the control population.

In general, the higher the velocity values the better was the reproducibility. The interobserver variation was as low as 10% for the PSV in the ophthalmic artery (with the highest velocities) and as high as 35% for EDV in the central retinal artery (the lowest velocities). In the case of the latter the velocity values were close to the resolution of the instrumentation and therefore undetected flow in the blood vessel may have been contributing to the poorer reproducibility. Resistive index provided more reproducible results because the errors in absolute velocity measurements induced by incorrect angle correction were reduced by the calculation of the ratio.

As expected interobserver variation was higher than intraobserver variation but the results from the two examinations by the two ultrasonographers were statistically similar. The results indicate that serial examinations in the same individual are best performed by the same ultrasonographer and that a difference in the velocity measurements of greater than 10-35% (depending on the blood vessel examined) indicate a 95 % chance of the change being true. There was a large interindividual variation (amongst the 95 volunteers) in the velocity results especially

at the lower velocity values. This variation reflects the fact that minor changes in blood vessel calibre can produce profound effects on the blood velocity. The normal ranges are wide, therefore, a disease will have to cause a severe change in blood velocity to produce a detectable result in an individual. An examination of occlusive diseases is required to determine whether changes in blood velocity can be detected. Another cause of variation in the results was the age of the volunteer but age corrected normal ranges were only applicable to the venous pulsatility index. The results were unaffected by the individuals sex or whether the eye was on the right or left, or by a history of arteriopathy (in a small group of volunteers).

3.5.1 THE BLOOD VESSELS.

INTRODUCTION.

In this part of the discussion the results of CDI of the control population are examined describing each blood vessel in turn. The effects of age, systemic parameters and posture are interpreted to allow an assessment of the properties of the blood flow in each vessel and to allow the reader to form a view of the relative usefulness of the examination of each blood vessel.

OPHTHALMIC ARTERY.

The ophthalmic artery was detectable in its course through the posterior orbit and in the nasal orbit. The velocity results from these two sites were statistically similar but a smaller range of values was found in the nasal orbit in which visualisation of the vessel and its direct course allowed angle correction to be applied more accurately. The ophthalmic artery is variable in its course in the posterior orbit, passing either above or below the optic nerve head and may have a dual supply from the internal carotid and middle meningeal artery, which anastomoses distal to this site ⁹⁹. For this reason after the initial examination measurements were taken from the nasal orbit. It may be argued, however, that readings from this site are of reduced relevance to the study of

ocular blood flow because the posterior ciliary and central retinal arteries have already branched off the ophthalmic artery before it reaches the medial orbit. The results from the ophthalmic artery were highly reproducible with approximately 10% variation in results from the same observer for PSV and resistive index and 22% for EDV. In the examination of the control cohort of 95 volunteers the ophthalmic artery velocities reduced with advancing age, perhaps an indication of the reduction in peripheral perfusion in the elderly. This was despite an increase in the incidence of systemic hypertension in the elderly group (PSV in the ophthalmic artery was positively correlated with systemic systolic blood pressure). Interestingly the PSV was lower in the patients who smoked than in those patients who were nonsmokers. The resistive index in this vessel was also lower in the smokers. This may have resulted from an effect of nicotine on the vessels constricting the peripheral vessels thereby reducing the peripheral blood flow, however this would also be expected to increase the peripheral resistance and therefore the resistive index. The difficulty in the interpretation of these results arises from the complexity of the effects of cigarette smoking on the vasculature which include arteriopathy and the effects of carbon monoxide (a cerebral vasodilator) and nicotine.

Change in posture to the supine position was expected to produce an increase in the velocities in the artery but although there was a trend for an increase in the velocities these did not reach significance. Canning and Restori using Duplex Doppler scanning in an undisclosed number of subjects found that there was an increase in the diastolic blood velocity in the supine position ²⁶. All future studies were performed with the subject in the supine position which was also the most convenient position for examination.

Central Retinal Artery and Vein.

The central retinal artery and vein are adjacent to each other in the optic nerve and therefore the measurements from these can be taken simultaneously. The vessels possess their straightest course in their intraneural portion allowing the application of angle correction with ease. As a result the reproducibility was good with variation between observations of 23-24% for the velocities (35% for EDV in the artery) from these vessels and 13-18% for the resistive indices. The resistive index increased with age probably signifying increased resistance to flow in the retinal arterioles in the elderly. Although the PSV increased with the systolic blood pressure in a similar fashion to the ophthalmic artery, postural changes induced no change in the velocities in the artery signifying the autoregulatory capacity of the retinal circulation.

Cigarette smoking also had no effect on this vessel. In the retinal vein an unusual pattern of pulsatile flow was seen. The venous pulsatile index was measured in the vein to provide a quantification of its pulsation. The values for this index do not provide a measure of the peripheral resistance of this vessel and should not be interpreted in such a way. Nor are they a measure of the resistance to flow upstream of the intraneural vein because the intraocular flow within the eye is reported as nonpulsatile ²³¹. Instead the results probably provide an indicator of the increase in the velocity of flow that is induced in the vein by the artery. This can be seen from the increase in the pulsatility index in the vein with age which follows the resistive index in the artery and by the positive correlation between the two indices from these vessels. The calculation of venous pulsatile index was increased primarily by an increase in the Vmax which may reflect the increase in velocity in the vessel caused by the proximity of the central retinal artery. This is in contrast to the arteries for which a reduction of the EDV caused an increase in the index and was a sign of the rapid reduction in blood velocity induced by high peripheral resistance.

Posterior Ciliary Arteries.

Investigators have reported that the posterior ciliaries are detectable by CDI ^{52,158} and duplex Doppler ⁹⁰. Results from these arteries have been reported in the literature in one control population and in disease groups but reproducibility data has not previously been provided. A hint of the poor reproducibility of the recordings from these blood vessels is evident from the extremely wide range of values obtained previously (1.4 - 22.7 cm/s) ¹⁵⁸. In this study, the reproducibility of the recordings from these vessels was poorer than the other orbital arteries. This is not surprising considering that they commence as a variable number of trunks (4-6) and then branch into 10-20 short posterior ciliary arteries ⁹⁹. The vessels are extremely tortuous and can often be detected during CDI as blood flow away from the globe indicating that they occasionally turn back upon themselves. Accurate angle correction in these circumstances is impossible resulting in poorer reproducibility. Although for the resistive index the variation was reduced measurements from these blood vessels are of limited value and their examination is best reserved to the observation of whether blood flow within them is present or absent.

Superior Ophthalmic Vein

Much has been made of the changes in the flow in the

superior ophthalmic vein in orbital diseases. For example reversal of flow has been assigned to diseases such as carotidocavernous fistula, tumours of the orbital apex and cavernous sinus thrombosis ^{13,52}. This investigation has determined that the blood in this vessel is not always detectable in the orbit, the vein may momentarily become undetectable. An arterial pattern of flow however does not occur normally and can be used to diagnose carotidocavernous fistula.

Vortex Veins

Four vortex veins are present one for each quadrant of the eye. An attempt was made to examine one on the temporal and one on the nasal side of the orbit but frequently it was difficult to detect these vessels.

The Inter Relationship of the Velocities in the Blood Vessels.

Not surprisingly the PSV or Vmax in a blood vessel positively correlated with the EDV or Vmin. The velocities in the central retinal artery positively correlated with the EDV in the ophthalmic artery but showed no correlation with the PSV in the ophthalmic artery. In turn the velocities and pulsatility index calculations from the central retinal vein positively correlated with the velocities and resistive index in the central retinal artery.

It was interesting to try to determine the influence of the velocity values on the calculation of resistive index. In the arteries the resistive index positively correlated with EDV. This reflects the influence of peripheral perfusion on the resistive index. If the peripheral resistance is high the velocity of the blood reaches a maximum in the systolic phase of the cardiac cycle as the blood is pumped out of the left ventricle of the heart but falls rapidly to a low velocity in diastole, in contrast the velocity remains high during diastole if the resistance is low. The values for pulsatility index in the vein were dependent on the value of Vmax, probably reflecting the influence of the central retinal artery on the vein, that is if the pumping action of the artery was large, the pulsation in the blood velocity induced upon the constant blood velocity of the vein was increased.

4 Chapter 4

DETERMINATION OF THE INTRAOCULAR PRESSURE (IOP) RISE PRODUCED BY ULTRASOUND EXAMINATION.

4.1 Summary

The application of an ultrasound transducer may induce intraocular pressure rises which may alter the blood flow in the eye. To investigate this potential source of error the intraocular pressure was monitored in an enucleated pig's eye during ultrasound examination. The elevations in pressure were small but variable depending on the ultrasonographer.

4.2 Introduction.

Blood flow in the retina is autoregulated up to intraocular pressure of 30 mmHg. Larger elevations in the IOP result in a reduction of blood flow. The ultrasound technique requires the application of a transducer to the closed eyelid of the patient. Although attempts are made to minimise the pressure being applied to the globe by resting the examiner's hand on the subject's orbital rim, intraocular pressure rises may occur. An experimental model was therefore designed to allow intraocular pressure (IOP) measurements during Bscan ultrasound and four different ultrasonographers were tested on repeated occasions to determine the degree of pressure elevation during the

examination and to see if there was any variation between operators or any effect of fatigue.

4.3 Method

A fresh pig's eye was supported in the orbital cavity of a human skull with an isosonic material and covered with a thin sheet of latex rubber (Supplied by Acuson ltd). Four ultrasonographers each performed five B scan ultrasound examinations of the globe and were asked to image the lens and posterior pole of the eye. A 5 to 10 second break was allowed between scans. A pressure transducer (Statham Strain Gauge Pressure Transducer) was inserted into the anterior chamber of the pig's eye to provide a continuous reading of the IOP during the examinations (Devices Instruments Ltd.). The ultrasonographers were masked from the results of the IOP measurements during imaging. The mean IOPs for each examination were determined to allow assessment of the IOP elevations caused by consecutive examinations and by the different ultrasonographers.

4.4 RESULTS

The mean intraocular pressure increases during the five examinations by the four ultrasonographers are shown in figure 4.1. The mean IOP rises induced by each examin-

Table 4.1
 Ultrasonographer. mean IOP rise (mmHg) Range
 (mmHg)

1	10.2	0 - 24
2	1.4	0 - 8
3	6.0	4 - 11
4	3.3	0 - 11

Table 4.1. The mean intraocular pressure rise and range of IOP rises induced in a pig's eye during Bscan ultrasonography by four ultrasonographers are shown. Considerable variation between the operators is apparent.

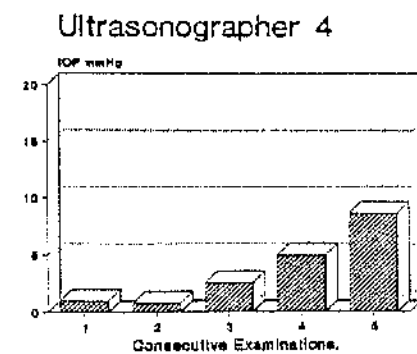
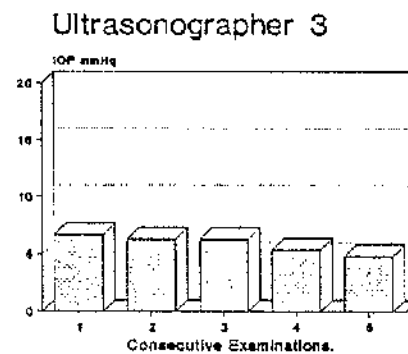
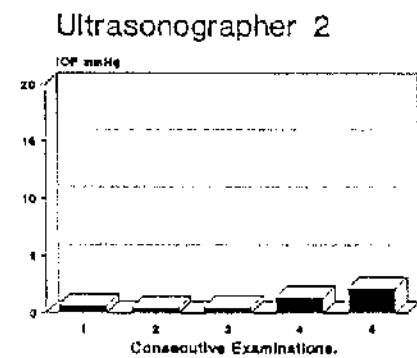
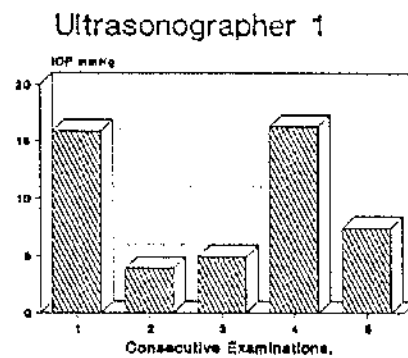


Figure 4.1. The intraocular pressure variations induced in an enucleated pig's eye during ultrasonography are shown for four ultrasonographers. The results from five consecutive examinations by each operator are provided.

er showed considerable variation (table 4.1).

Ultrasonographer 2 and 4 induced the lowest intraocular pressure rises and have performed all of the colour Doppler imaging in the studies of control populations and disease processes described in this paper.

Discussion.

External pressure from the ultrasound transducer may potentially result in an increase in the intraocular pressure during examination. It is important during Doppler imaging to minimise this external pressure so as to reduce any effect on blood flow. We have determined that there is considerable variation in the intraocular pressure rises induced by different ultrasonographers. With the exception of two operators, the elevation in IOP was limited to a maximum of 11 mmHg and the mean rises were small. Previous animal experimentation has shown that the retinal blood flow remains stable during moderate rises in intraocular pressure ^{2,72} and in humans Riva et al (1986) using laser Doppler velocimetry showed that blood velocity in the retinal circulation is effectively autoregulated up to intraocular pressures of 32 mmHg ²²⁹. It would appear, therefore, that the small intraocular pressure rises produced during the ultrasound examination are unlikely to influence blood flow velocity measurements.

5 Chapter 5

EXAMINATION OF PATIENTS WITH ARTERIAL OCCLUSION OF THE BLOOD VESSELS OF THE OPTIC NERVE HEAD.

5.1 Summary

Multiple arteries were apparent at the optic nerve head providing colour indices of flow in this region on colour Doppler imaging. These could presumably be identified as posterior ciliary arteries and the central retinal artery by their anatomical relationship to the optic nerve but to substantiate their identity patients with known occlusion of these vessels were examined. The central retinal artery was found to provide colour indices in the optic nerve shadow whilst the posterior ciliary arteries produced peripapillary indices. The results further illustrated the difficulty in accurately measuring from the posterior ciliary arteries.

5.2 Introduction.

It was apparent that CDI of the arterial vasculature of the optic nerve head region involved multiple vessels. The central retinal artery is anatomically located within the optic nerve with 10 to 20 posterior ciliary arteries surrounding the optic nerve. Although it was assumed that these vessels could be identified either by anatomical location or by the identification of

blood flow in the region on CDI, confirmation of the identity of these vessels was required. Therefore, to investigate the contribution of the posterior ciliary and central retinal arteries to the measurements from this region patients with known occlusion of these vessels were imaged. Patients with central retinal artery occlusion and anterior ischaemic optic neuropathy (occlusion of the posterior ciliary arteries) were examined in the acute stage of the process, ie., within twenty four hours of the onset of symptoms. The blood velocity characteristics of these occlusive disorders was further investigated by performing serial examinations and also by imaging patients with at least a 3 weeks interval from their onset of the occlusion, the results from which are presented more fully elsewhere ³⁰⁰.

5.3 Patients and Methods

Fourteen patients were examined who had suffered either acute anterior ischaemic optic neuropathy (AION, seven patients) or central retinal artery occlusion (CRAO, seven patients). CDI was performed by an observer who was masked from the clinical diagnosis of the patients. All patients were fully informed and consented to the procedure. Velocity recordings were obtained from the ophthalmic artery and its continuation in the medial

orbit and from the optic nerve head. Only if three consecutive pulse waveforms could be obtained from a site showing color indices was this site deemed a reliable source for velocimetry.

The patients had a detailed history taken for the clinical features of giant cell arteritis. Systemic blood pressure, erythrocyte sedimentation rate (ESR) were recorded. Temporal artery biopsies were performed on all patients with anterior ischaemic optic neuropathy and three patients with central retinal artery occlusion who exhibited raised ESRs or clinical features consistent with the diagnosis of cranial arteritis.

Fundus fluorescein angiography using a wide angle Canon Fundus camera was performed within 24 hours of Doppler ultrasonography on all cases with acute arterial occlusion (see section 9.3). The fluorescein angiograms were assessed by an independent observer, masked to the patients' identities, clinical diagnoses or velocimetric recordings. Color Doppler examinations were repeated in six patients with evidence of arterial nonperfusion to determine the time-course of reperfusion.

Four patients with acute CRAO were examined by Doppler velocimetry within 24 hours of the onset of visual loss. A further three patients were examined who had suffered from CRAO at least three weeks earlier.

Similarly, four patients with AION of arteritic (three patients) or non-arteritic types (one patient) were examined within 24 hours and three were examined whose vascular occlusions had occurred more than three weeks previously.

5.4 RESULTS.

None of the patients with CRAO had a positive temporal artery biopsy. In three patients with acute central retinal artery occlusion no blood flow was detectable in the central optic nerve. Peripapillary colour indices of flow were present (table 5.1, figure 5.1). Although occasional pulse velocimetry readings were obtainable from these sites no reproducible measurements (three consecutive pulse waveforms) could be obtained. Fluorescein angiography in these patients confirmed the diagnosis and revealed an intact posterior ciliary circulation as evidenced by normal choroidal and optic nerve head perfusion (table 5.2). Doppler studies in three patients with acute anterior ischaemic optic neuropathy showed no detectable peripapillary colour indices but did show evidence of a central vessel at the optic nerve head (table 5.1, figure 5.2). Velocimetry measurements were obtained from the optic nerve head in all of these patients. All three had positive temporal artery biopsies.

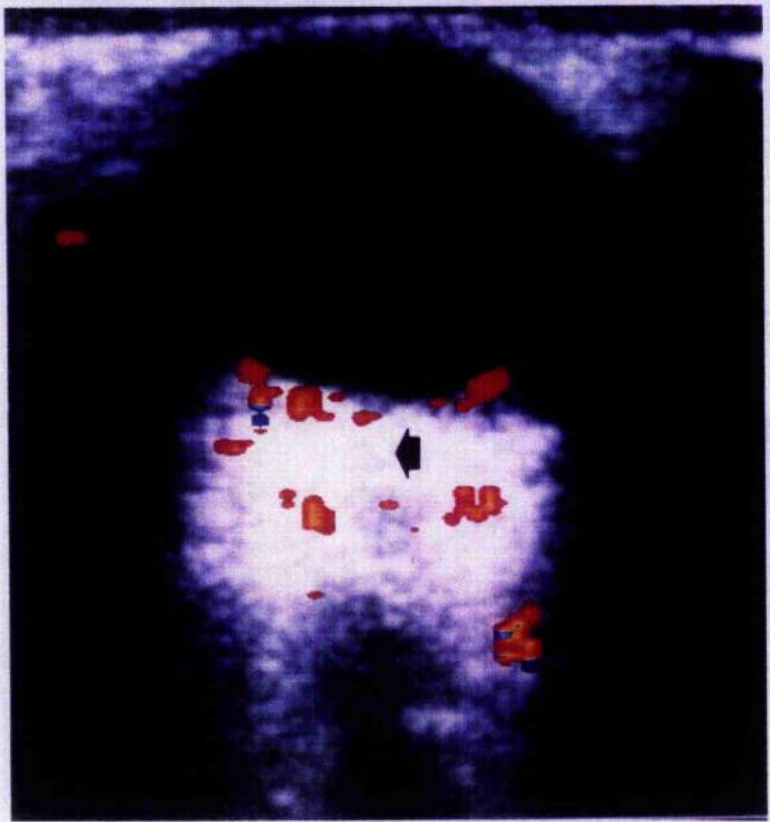


Figure 5.1. The color Doppler image is provided for a patient with central retinal artery occlusion on whom no flow was detectable within the optic nerve (arrow).

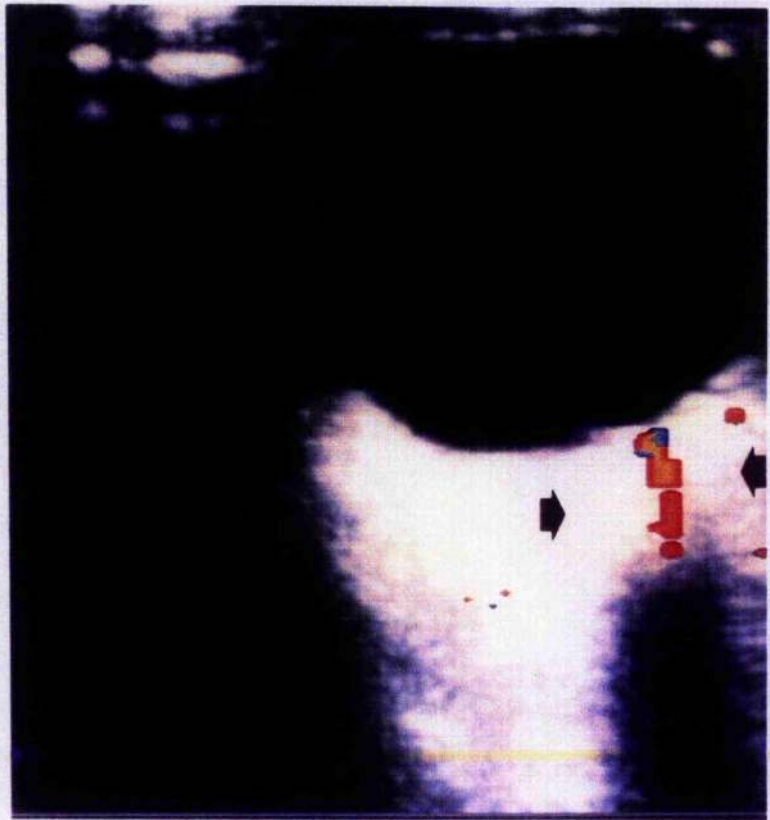


Figure 5.2. The color Doppler image is provided for a patient with anterior ischaemic optic neuropathy in whom no perineural flow was detectable (arrow).

Table 5.1

Case	Diagnosis	Optic Nerve	Tm _{vf} (secs)	Choroid/Retina (secs)
1	CRAO	Normal	38.1	0.0
2	CRAO	Normal	11.2	3.5
3	CRAO	Normal	35.8	5.4
4	AION	No inferior fill.	6.5	0.0
5	AION	No inferior fill.	6.6	-4.6
6	AION	No inferior fill. delay superiorly.	8.2	-6.8

Table 5.1. The results of fluorescein angiography of eyes with abnormal position 3 (optic nerve head) scans for patients with central retinal artery occlusion (CRAO) and anterior ischaemic optic neuropathy (AION). Results are shown of the masked assessment of optic nerve head perfusion, time to maximal venous filling of dye (tm_{vf}) and time to choroidal perfusion relative to the first appearance of dye in retinal arterioles (a negative result indicates choroidal filling after retinal arteriolar filling).

Table 5.2

Case	Diagnosis	Central Retinal Artery PSV cm/sec	EDV cm/sec	RI %	Posterior Ciliary Arteries
1	CRAO	NIL	NIL	NIL	YES
2	CRAO	NIL	NIL	NIL	YES
3	CRAO	NIL	NIL	NIL	YES
4	AION	7.4	3.0	59	NO
5	AION	4.6	1.4	69	NO
6	AION	5.6	1.4	75	NO

Table 5.2. The results of colour Doppler imaging of eyes with abnormal (optic nerve head) scans for patients with central retinal artery occlusion (CRAO) and anterior ischaemic optic neuropathy (AION). Peripapillary colour indices of flow were either detectable (YES) or undetectable (NO).

Fluorescein angiographic evidence of normal dye transit times confirmed the presence of normal central retinal artery perfusion in these patients. Delayed choroidal filling and absent optic nerve head perfusion provided evidence for reduced posterior ciliary artery circulation (table 5.1).

The Doppler results at the optic nerve head were normal in all six patients whose vascular occlusion had occurred more than three weeks earlier. A normal recording was also obtained from one patient with acute CRAO and one with acute AION (temporal artery biopsy showed no evidence of cranial arteritis in this patient). Fluorescein angiography demonstrated that perfusion of the retinal and posterior ciliary arterial circulations had been restored in these patients (table 5.1).

Blood velocities were detectable in the ophthalmic artery of all patients but was retrograde in one patient with CROA.

5.5 Discussion.

Doppler velocity readings were absent at the optic nerve head in cases of acute CRAO in which hypoperfusion of the retinal circulation was present on fluorescein angiography evidenced by markedly prolonged arterio-venous dye transit times. These cases showed absence of color indices of flow in the central portion

of the optic nerve. Peripapillary color indices were visible from blood flow in the posterior ciliary arteries but did not provide reliable velocimetry readings. Carotid artery disease is not uncommon in patients with CRAO ²¹² and its presence in these patients might have caused a reduction of perfusion of the posterior ciliary circulation thereby explaining our findings. Indeed a patient with internal carotid occlusion has been reported in which absent perfusion on CDI of the nasal posterior ciliary arteries and central retinal artery was interpreted as a partial occlusion of the ophthalmic artery ¹⁵⁹. In this case the velocity of blood flow was also reduced in the ophthalmic artery. The determination of normal blood velocity in the ophthalmic artery in six out of seven of our patients with CRAO suggested the presence of a normal blood supply to the orbit from the internal carotid circulation. The remaining patient demonstrated perfusion of the ophthalmic artery which was probably via the external carotid circulation. The failure of CDI to provide reliable measurements from the posterior ciliary arteries in these patients therefore provides further evidence that these vessels provide unreliable velocity results and their assessment should be restricted to the determination of the presence or absence of flow. Three of the patients with acute AION showed a single

central blood vessel in the region of the optic nerve head but did not show evidence of blood flow within the multiple peripapillary blood vessels with CDI. All of these patients were suffering from giant cell arteritis. Absent or reduced blood flow in the posterior ciliary arteries was confirmed by the demonstration of incomplete optic nerve head perfusion on fluorescein angiography. Velocity readings at the optic nerve head were measurable from the centrally placed artery, the central retinal artery.

Those cases of AION examined in this study produced interesting results. Of the four patients examined within 24 hours of occlusion, three with arteritic AION showed loss of the indices of flow in the posterior ciliary arteries. The remaining patient with a non-arteritic AION showed detectable peripapillary blood flow. Hayreh has argued for the occurrence of a temporary occlusion in the non-arteritic form of AION which may explain why normal flow was detected in this individual ¹⁰². Alternatively, there may have been only partial occlusion of the posterior ciliary circulation.

In one patient with giant cell arteritis loss of flow in the whole orbit was seen at a later stage in the disease process and demonstrates the more extensive nature of the arteritic process. This was associated, in this case, with a deterioration in the course of the disease despite what was deemed to have been appropri-

ate therapy. This more global reduction in orbital blood velocity in the arteritic form of the disease may provide a useful discriminator from the non-arteritic type of AION. It may also explain why there is reduced ocular blood flow seen with ocular pneumo-plethysmography in the arteritic form of AION but not the non-arteritic form ²⁰. Whether colour Doppler ultrasound will be of use in the investigation of cranial arteritis needs further study. Although it has been applied to the examination of the temporal arteries to detect retrograde flow before biopsy ²⁸⁹, it has not to our knowledge been used to aid diagnosis.

6 Chapter 6

AN UNDERSTANDING OF THE RETINAL CIRCULATION PROVIDED BY AN ANOMALOUS RETINAL VEIN

6.1 Summary

The velocities obtained from the central retinal vein demonstrated an unusual pulsatile waveform which may have occurred from the close approximation of the vein to the central retinal artery in the nerve or from intraocular pressure variations in the eye. A patient was examined by CDI in whom one hemiretinal vein passed outwith the nerve and the other within the nerve. Only in the latter was a pulsatile waveform observed suggesting that the location of the vein within the nerve is required for the production of pulsatile flow in the vein.

6.2 Introduction

In the study of the control population the blood velocities in the central retinal vein in the optic nerve have been found to have an unusual pulsatile pattern of flow which is in synchrony with the arterial pulse (figure 3.4) and which is not seen in other veins. This pattern of blood flow may occur because the intraocular venules are compressed by the fluctuations in pressure within the eye which occur with the systemic pulse. Alternatively, the reason may

be the close approximation of the vein to the central retinal artery in the distal optic nerve where both vessels are enclosed within a common adventitial sheath. A colour Doppler examination from a patient with an unusual retinal venous anatomy facilitated the identification of the source of the pulsatile velocities in the vein.

6.3 Case Report

A 61 year old man was noticed on fundoscopy to have a superior hemiretinal vein which directly entered the choroid adjacent to the upper edge of the optic disc (figure 6.1). The inferior hemiretinal vein followed the usual path and entered into the central optic disc with the artery.

Colour Doppler imaging was used to detect the blood velocity signals from the continuation of the inferior hemiretinal vein within the optic nerve adjacent to the central retinal artery. Spectral analysis of these signals provided a pulsatile velocity waveform which was in synchrony with the pulsations in the central retinal artery and which was similar to the waveforms from the central retinal vein of normal controls with a maximum velocity of 8 cm/sec and a minimum velocity of 5 cm/sec. The Doppler signal attributable to the superior hemiretinal vein was detected in the



Figure 6.1. The retinal venous pattern is shown with the superior hemiretinal vein appearing to enter into the choroid adjacent to the optic nerve (arrow). The inferior hemiretinal vein enters into the central optic disc with the arteries.

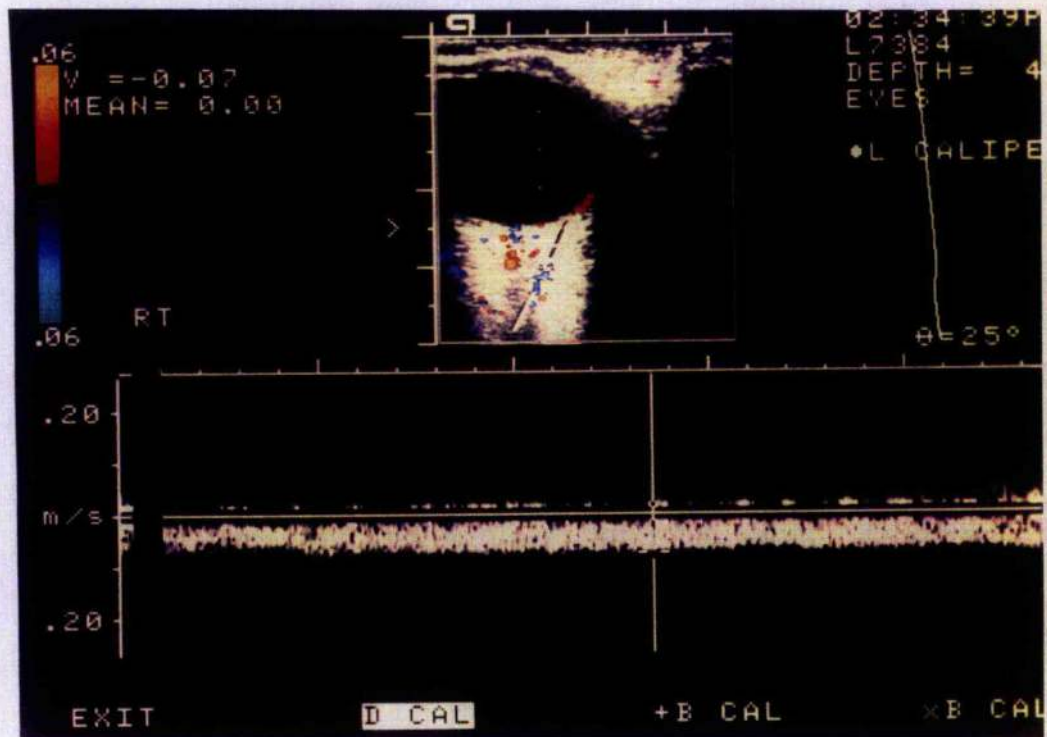


Figure 6.2. The colour Doppler image of the right orbit showing the superior hemiretinal vein (extraneural) and the spectral analysis of the blood velocities in this vessel which demonstrates a nonpulsatile waveform.

perineural area at the level of lamina cribrosa and continued down the side of the optic nerve to join the inferior hemiretinal vein as it exited the nerve approximately 10mm posterior to the globe (figure 6.2). The waveform in this vessel exhibited a constant peak velocity of 7 cm/sec and did not manifest the normal central retinal venous pulsatile waveform.

6.4 Discussion.

This case demonstrates that an extraneural retinal vein has a constant flow rate, whilst an intraneural retinal vein exhibits a pulsatile flow rate in phase with the cardiac cycle. If the fluctuations in the intraocular pressure were responsible for the pulsations in the vein both the intraneural vein and the extraneural vein would have been expected to possess pulsatile flow. Since only the intraneural vein had pulsatile flow this must have been induced by the anatomical location of the vein within the nerve. The central retinal artery and vein in the optic nerve share a space within a common adventitial sheath ²⁶⁹. This sheath which has a relatively broad diameter and is collagenous, is relatively indistensible. The dilation of the artery within this confined space during systole must result in compression of the vein. We speculate that this may have the effect of "pumping" blood into the distensible distal vein as it leaves the optic nerve thereby resulting in the pulsatile blood flow rate which has

been observed.

7 Chapter 7

THE RELATIONSHIP BETWEEN BLOOD VISCOSITY AND OCULAR BLOOD FLOW.

7.1 Summary

In a cohort of volunteers who underwent CDI examination of their orbital vessels various systemic measures of blood viscosity were obtained. The results demonstrated that there were correlations between the viscosities and the measures of peripheral resistance in the blood vessels as estimated by resistive index calculations. It would appear that in the normal population increased viscosity is compensated for by a reduction of peripheral resistance perhaps by peripheral vasodilation.

7.2 Introduction.

The Hagen Poiseuille law indicates that the flow of a fluid in a tube is reduced when the viscosity of the fluid increases. It is likely therefore that ocular blood flow will be affected if the blood viscosity is altered ²⁰⁵. Indeed in an experimental model using the pig, retinal blood flow was found to reduce as the blood viscosity increased ⁷.

Blood viscosity is particularly important in the venous

system where slower blood flow causes a relative increase in viscosity resulting in a susceptibility to stasis 168,169,203. This in turn may result in thrombus formation further reducing the blood flow. Indeed blood viscosity has been implicated in the pathogenesis of retinal venous occlusion of the eye 60,173.

Viscosity is calculated from the shear stress (force being applied to a fluid) and the velocity of the fluid.

$$\text{Viscosity} = \frac{\text{Shear Stress}}{v_2 - v_1 \text{ (Velocity Difference)}}$$

Blood plasma demonstrates Newtonian properties of viscosity in that the blood velocity is directly proportional to the shear stress applied. Plasma viscosity is measured using a capillary viscometer which measures only at one shear stress. Whole blood shows non-Newtonian characteristics, ie., the viscosity increases at low shear stresses. Cylindrical or conical viscometers are often used which allow measurement of whole blood viscosity at different shear stresses but if such measurement is to be taken at only one shear stress a capillary viscometer can be used. Whole blood shows an additional increase in viscosity at very low shear stresses. This change in viscosity is described as "pseudoplastic" because plastics have the property of becoming solid at low shear stresses. Plasma viscosity is increased by elevated plasma

protein levels, globulins having the greatest effect, followed by albumin and then fibrinogen ²⁰³, and whole blood viscosity rises with elevated haematocrit, fibrinogen, plasma viscosity, erythrocyte aggregation or by reduced erythrocyte deformability. In turn, erythrocyte aggregation increases with elevated plasma levels of IgM, IgA and alpha 2 macroglobulin. Abnormalities of rheology have previously been detected in a variety retinal vascular and ocular disorders (table 7.1). In this study the relationship between systemic viscosity and orbital blood velocities from Doppler imaging in normal individuals was investigated.

7.3 METHOD

Twenty four of the volunteers from the control population examined in the colour Doppler experiments had blood rheology examined on the same day as their colour Doppler imaging. Venous blood was sampled from an antecubital vein with a 21 gauge butterfly needle after minimal use of a tourniquet. Blood was anticoagulated with dipotassium edetate (K2 EDTA, 1.5mg/ml) for viscosity examination which was performed within four hours of sampling. Whole blood viscosity and plasma viscosity were measured at high shear rates (more than 300/sec) in a capillary viscometer (Coulter-Harkness) at 37 degrees C. Haematocrit (Hawksley

7.1. Ocular Disorders and Rheology.

Retinal Vein Occlusion.

See table 11.1.

Diabetic Retinopathy.

Blood viscosity has been found to be higher in patients with diabetic retinopathy compared with controls ^{10,119,211} and may be due to increased erythrocyte aggregation ^{244,274} or reduced erythrocyte deformability ¹⁰ or reduced leucocyte filterability ²⁸⁸. Increased severity of retinopathy has been associated with significantly higher whole blood viscosity, plasma viscosity and fibrinogen in some studies ^{170,171} but not in others ^{8,119,211,234}. In addition, blood from patients with retinopathy demonstrates increased viscosity during hypoxia in a similar manner to sickle cell disease ²²⁶.

Sickle cell retinopathy.

No differences in viscosity or erythrocyte filterability between patients with sickle cell-haemoglobin C and homozygous sickle cell disease with and without proliferative retinopathy ^{248,249}.

Vasculitis.

Plasma viscosity measurements provide an alternative to erythrocyte sedimentation rate in the diagnosis of cranial arteritis ²³.

Immunosuppressive therapy (including plasmapheresis in one patient) reduced the plasma viscosity and retinopathy in two patients with retinal vasculitis ³².

Central retinal artery occlusion.

Six patients had increased plasma viscosity, fibrinogen, erythrocyte aggregation and reduced erythrocyte deformability compared to normal values ¹³⁰.

Malignant hypertension.

No difference in rheological variables in malignant hypertension compared with nonmalignant hypertensives were found. Inhibitors of plasmin, fast antipiasmin and alpha₂ macroglobulin, were increased suggesting reduced fibrinolytic activity ¹¹⁹.

AIDs.

High fibrinogen levels are detected in patients with cotton wool spots ⁵¹. A patient with vasculitis responds to therapy, see above ³².

Eales Disease.

A retrospective study determines that plasma viscosity, erythrocyte rigidity and erythrocyte aggregation are significantly increased in the acute stage of the disease and reduces as disease activity reduces ¹⁵.

Glaucoma

Increased whole blood and plasma viscosity was detected in one controlled study of patients with low tension glaucoma ¹³² but not in another study ²⁸. Patients with primary open angle glaucoma but not those with ocular hypertension were found to have raised mean blood viscosity compared to controls ⁶⁸.

Age related macular degeneration.

No difference in rheology was observed in 35 patients with age related macular degeneration compared with 35 controls ¹¹⁷.

microhaematocrit, 13000 g for 5 minutes) and red cell aggregation (photometric aggregometer, Myrenne GmbH, Roetgen, Germany) were also recorded and haematocrit corrected and relative blood viscosity calculated ¹⁷²:

$$CBV = PV \times (\text{EXP} (\log WBV/PV \times 45/HCT))$$

$$RBV = CBV/PV$$

CBV = Haematocrit Corrected Blood Viscosity

RBV = Relative Blood Viscosity

PV = Plasma Viscosity

WBV = Whole Blood Viscosity

HCT = Haematocrit

The haematocrit has a profound effect upon the measurement of whole blood viscosity. Therefore haematocrit corrected blood viscosity was calculated to provide a measure of the blood viscosity from factors other than haematocrit. In turn the relative blood viscosity was used to determine the relative contribution of plasma viscosity and cellular deformability or aggregation on the viscosity.

7.4 RESULTS

Table 7.2 shows the mean viscosity values for the volunteers. Multivariate linear regression analysis

Table 7.2

	mean	SD
Whole Blood Viscosity (mPas)	3.4	0.7
Plasma Viscosity (mPas)	1.3	0.1
Haematocrit (%)	43.3	4.3
Red Cell Aggregation	4.8	0.9
Corrected Blood Viscosity (mPas)	3.4	0.5
Relative Blood Viscosity	2.6	0.3

Table 7.2. The results of the examination of the various viscosity parameters in the comparison with the blood velocities in the orbital vessels.

was employed with the variable "age" of the patient because this had been found to affect the Doppler velocities (see section 3.4.4). Systolic blood pressure was also included when analysing the ophthalmic artery velocities. Whole blood viscosity and haematocrit were negatively correlated with the resistive index in the ophthalmic artery (both $b=-0.55$, figure 7.1 and 7.2). Haematocrit corrected and relative blood viscosities were significantly negatively correlated with the venous pulsatility index in the vein ($b=-0.43$ and $b=-0.34$ respectively, figure 7.3 and 7.4). No correlations were found between the viscosities and the velocity measurements from the central retinal arteries.

7.5 DISCUSSION

In this study, haematocrit corrected and relative blood viscosity were negatively correlated with the venous pulsatility index in the central retinal vein. Using the venous pulsatility index as a measure of pulsatility, increased relative blood viscosity (indicating reduced cellular deformability or increased red cell aggregation) appears to reduce the pulsations in the vein. Whether this effect on pulsatility of the flow in the vein is detrimental to the flow of blood in the central retinal vein and thus increases the risk of

Ophthalmic Artery RI and Whole Blood Viscosity

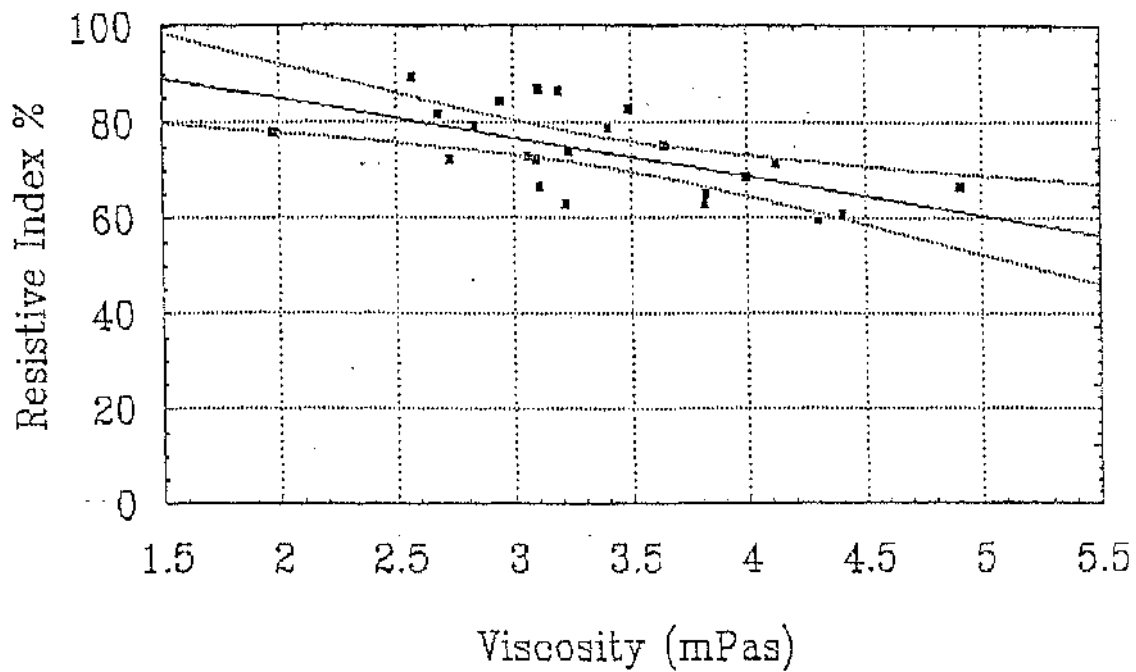


Figure 7.1. The resistive index in the ophthalmic artery negatively correlates with whole blood viscosity (linear regression lines are shown with 95% confidence limits).

Ophthalmic Artery RI and Haematocrit

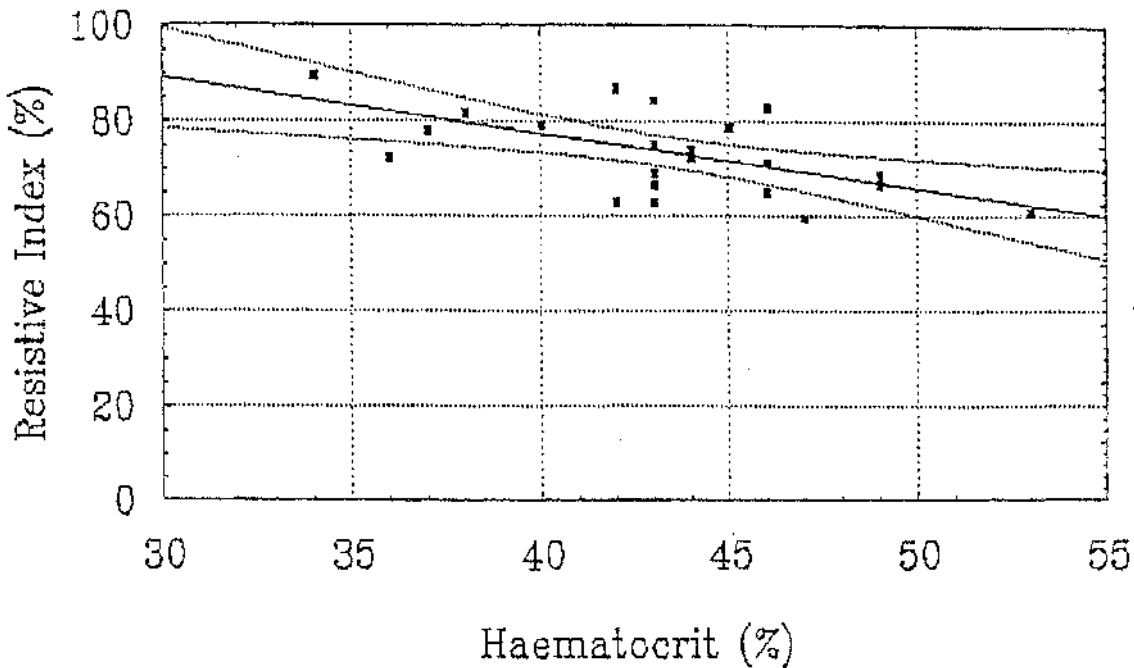


Figure 7.2. The resistive index in the ophthalmic artery negatively correlated with the haematocrit (linear regression lines are shown with 95% confidence limits).

Retinal Vein Pulsatility and Corrected Blood Viscosity

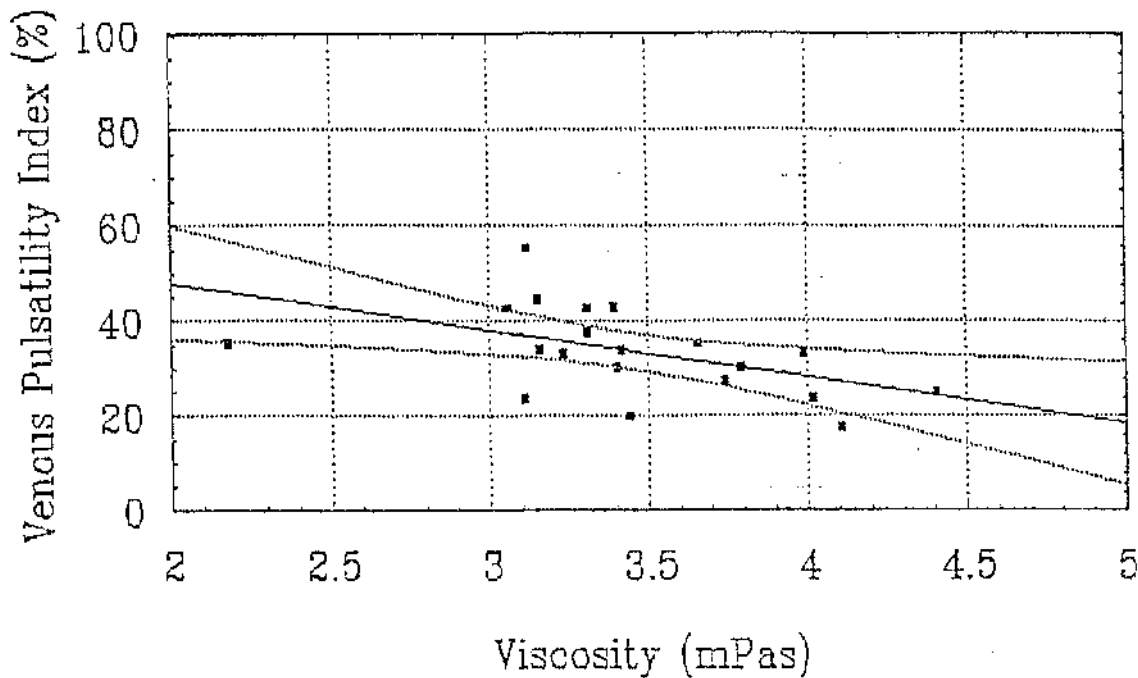


Figure 7.3. The venous pulsatility index in the central retinal vein negatively correlated with haematocrit corrected blood viscosity (linear regression lines are shown with 95% confidence limits).

Retinal Vein Pulsatility and Relative Blood Viscosity

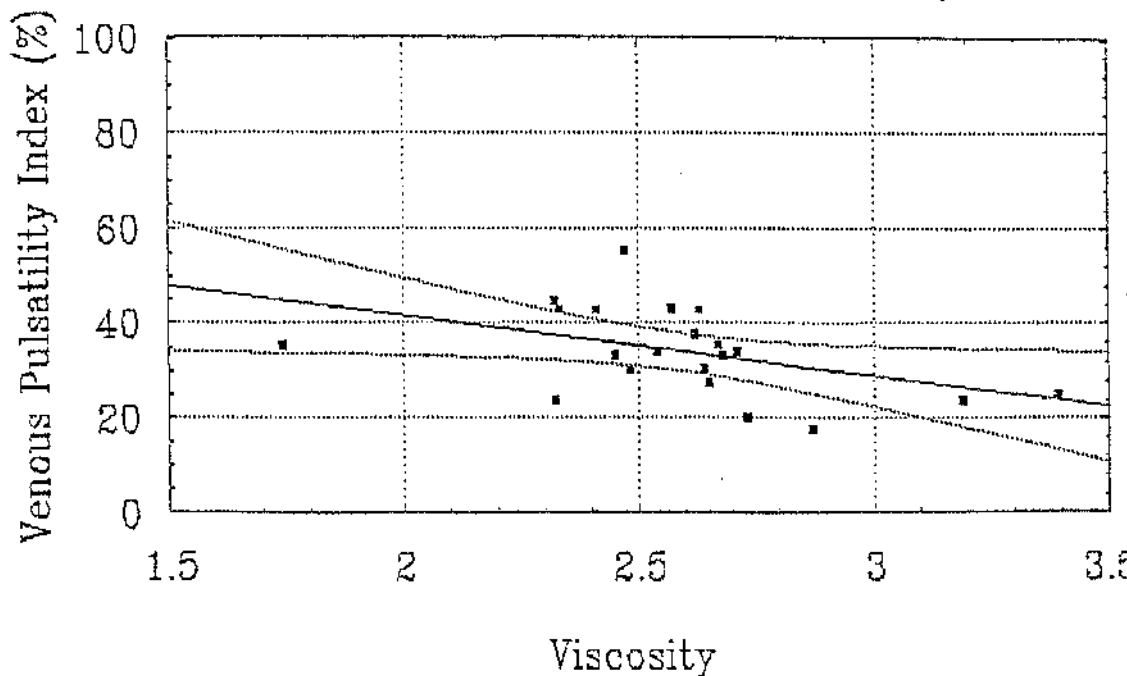


Figure 7.4. The venous pulsatility index in the central retinal vein negatively correlated with elevated relative blood viscosity (linear regression lines are shown with 95% confidence limits).

stasis or occlusion remains to be seen.

In this study, the viscosity results did not influence the values for blood velocity in the orbital arteries perhaps because of compensation for elevated viscosity by vasodilation but the resistive index from the ophthalmic artery demonstrated a negative correlation with the haematocrit and whole blood viscosity. The resistive index can be reduced by both increased resistance to flow upstream of the measurement site and also by decreased resistance to flow downstream. Since haematocrit is the most important determinant of blood viscosity in arteries of greater diameter than 300 microns (the ophthalmic artery has a diameter of approximately 300 microns) but becomes relatively unimportant in smaller arteries and arterioles, the changes in the values may have arisen from increased resistance to flow in the carotid circulation. An alternative interpretation is that the blood viscosity has induced peripheral vasodilation thereby reducing peripheral resistance to flow and maintaining the blood velocities.

These findings indicate that there is a relationship between ocular blood flow and viscosity. Studies of this relationship in patients with central retinal vein occlusion are described in chapter 11.

8 Chapter 8

INTRODUCTION TO CENTRAL RETINAL VEIN OCCLUSION

8.1 Summary

A critical review is provided of the literature on the subject of central retinal vein occlusion (CRVO). The results of pertinent investigations are discussed to allow an appreciation of the aims of the studies of blood velocity and viscosity in future chapters.

8.2 Introduction.

Central retinal vein occlusion is a common vascular disorder of the eye which results in a rapid onset of loss of vision and ultimately may lead to a blind, painful eye. The condition is characterised by dilation of the retinal veins and widespread retinal haemorrhages with, in many instances, a swollen optic disc (figures 8.1 and 8.2, table 8.1). The vitreous is more often detached in the ischaemic form of the disease and the incidence of vitreomacular attachment is said to be higher in those patients who develop cystoid macular oedema ¹²⁵.

Since the first description in 1870, there has been much debate concerning the pathogenesis (table 8.2) ¹⁹⁴. Even today there is still uncertainty whether the disorder is primarily due to occlusion of the central retinal vein or occlusion of the central retinal ar-

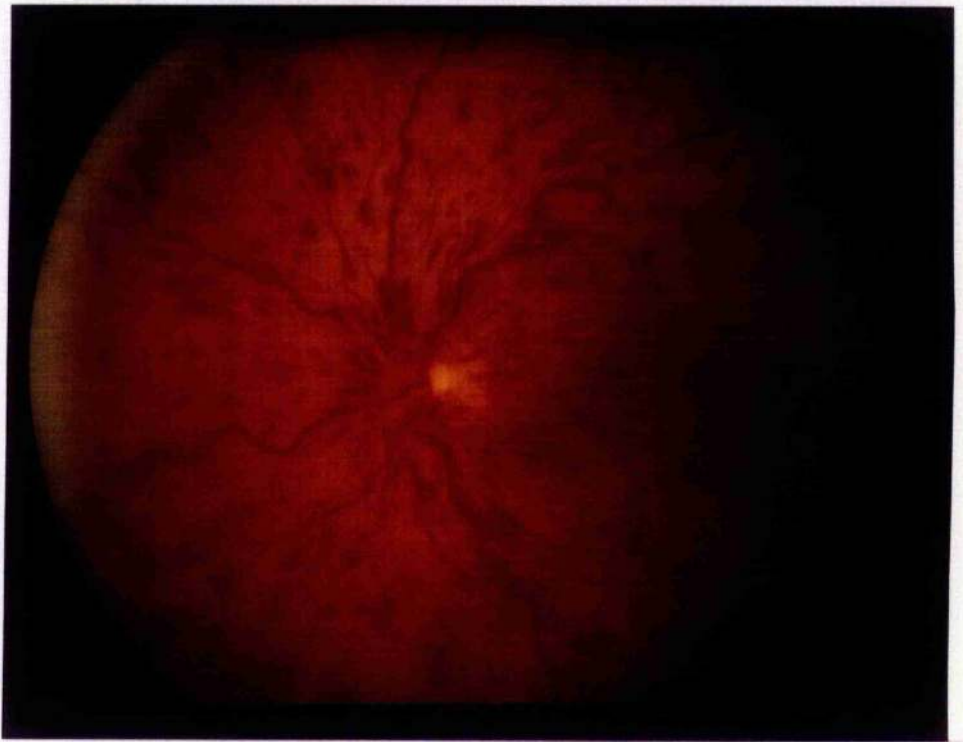


Figure 8.1. A fundus photograph of the retinal appearance of a nonischaemic CRVO.

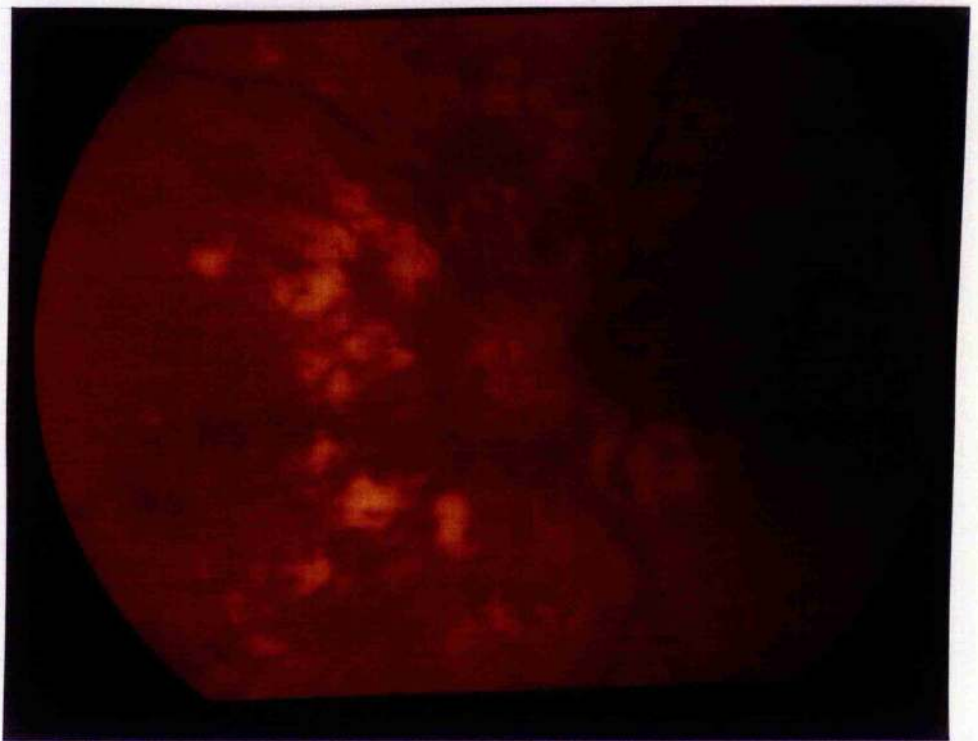


Figure 8.2. A fundus photograph of the retinal appearance of an ischaemic CRVO.

Table 8.1
Clinical Features.

Moore, 1924; Braendstrup, 1950 21,200.

Most common in the 7th decade.

Males equal females.

Left eyes more than right.

Sudden loss of vision, occasionally gradual onset.

Dim or misty vision described.

Most present in within 3 months of onset.

Visual acuity can be moderately or markedly reduced, usually becoming progressively worse.

Intraocular pressure is lower in the affected eye.

Ophthalmoscopic Features

Retinal oedema

Dilated and tortuous veins.

Profuse retinal haemorrhages (superficial and deep)

Microaneurysms

Cotton wool spots

Disc hyperaemia and swelling

Late Features

Disappearance of retinal haemorrhages and cotton wool spots.

Macular degenerative changes

Neovascularisation of the disc, retina or iris.

Table 8.2

Historical Review of Central Retinal Vein Occlusion.

Liebreich, 1855 Describes the clinical appearance of CRVO as retinal apoplexy ¹⁸².

Leber, 1877 Describes CRVO as haemorrhagic retinitis ¹⁵⁵.

Michel, 1878) The first published report of the pathological findings in CRVO. 2 cases were described one with proliferation of the intima and the other ascribed to thrombus formation in the vein ¹⁹⁴.

Coats, 1904 Describes 4 cases pathologically, 3 thought to be due to thrombi and one to endothelial proliferation. He believed on review of the cases described so far that angiosclerosis was a significant association with CRVO (and noted an association with mitral stenosis). Plates show a crescentic shaped vein. The eyes were rubeotic ³⁵.

Harms, 1905; Leber, 1915; Klien, 1944 Believe that stagnation of the central retinal artery blood flow causes secondary thrombosis and obstruction of the central retinal vein ^{95,134,156}.

Verhoeff, 1906 Reviews 39 cases previously described in the literature, concluding that only 2 have pathological evidence of thrombosis and that these cases may have resulted from sepsis. He considers the blockage to be due to intimal thickening and degeneration with a resultant formation of a "collateral" vein through the vein wall in the fashion of a dissecting aneurysm ²⁸⁴.

Coats, 1913 Discussion on retinal vascular disease outlining similar topics of argument which exist today, eg., the roles of thrombosis within the vein and hypoperfusion of the arterial circulation, life expectancy after CRVO, the role of inflammation or systemic diseases ³⁶.

Verhoeff, 1913 Describes the change of endothelial cell proliferation and "dissecting aneurysm" of the vein in eyes with open angle glaucoma, therefore, concluding that these effects are solely due to raised iop and not a result or cause of CRVO ²⁸⁶.

Moore, 1922 Measures iop in CRVO and notes that the affected eye has a reduced iop in comparison to the fellow eye ¹⁹⁹.

Moore, 1924 Describes the typical features of the condition in a series of 62 patients. Describes young patients with influenza and CRVO ²⁰⁰.

Verhoeff, 1907 Suggest that collateral circulations are important in the protection of the retina from damage in CRVO, eg., opticiliary veins, cilioretinal veins, choriovascular veins ²⁸⁵.

Harms, 1905; Moore, 1924; Klien, 1944; Gradle, 1937 Believe that congenital vascular anomalies play a role in the pathogenesis of CRVO ^{78,95,134,200}.

Gradle, 1937 Suggests that the vein leaves the nerve too early. Uses Xray therapy in 9 patients with no effect on the retinal appearance of CRVO ⁷⁸.

Klien, 1944 Examines pathologically 21 cases of CRVO removed for glaucoma and shows that in patients with systemic disease most endothelial cell proliferation occurred in the anterior or prelaminar portion of the vein secondary to a mechanical retrolaminar narrowing, whereas in the elderly and those without systemic disease proliferation occurred primarily in the posterior lamina ¹³⁴.

Verhoeff 1940 A case of tubercle of the central retinal vein associated with haemorrhagic retinopathy ²⁸⁷.

Braendstrup, 1950 Large series describing the clinical features of the disorder. Cases of CRVO in infections of the paranasal sinuses, cavernous sinus thrombosis, facial erysipelas, ophthalmic herpes zoster, polycythaemia and leukaemia 21.

Bruker, 1945 Cases of CRVO secondary to direct trauma 24.

Mancall, 1951 A review of the pathological literature with the contention that in elderly patients the occlusion is due to endothelial cell proliferation and in those with systemic inflammatory or infective disease it is due to thrombophlebitis 178.

Larsson, 1950 The first description of a series of patients with CRVO treated with anticoagulation. An uncontrolled study of 59 cases treated with dicoumarin and heparin showing results suggesting that such treatment is ineffective 154.

Vannas 1966 A review of the literature and description of a large series of patients with CRVO treated by anticoagulation. A nonrandomised controlled study of 179 patients using heparin and prothrombin depressants. Most series have shown no definite benefit 282.

Dobree, 1957 Detects CRVO in 4.5% of 200 eyes with primary open angle glaucoma and in 4% of 150 eyes with arteriosclerosis. A difference was noted from the results of branch vein occlusion which was found in 1% of glaucoma patients and 7.3% of patients with arteriosclerosis 39.

Vannas 1960 Performs a tonographic study of the incidence of primary open angle glaucoma in CRVO finding the condition in 42% of patients 283.

Paton, 1964 Describes the fluorescein angiographic appearance of CRVO 208.

Henkes, 1953 The first large series on electroretinography in CRVO with 83 cases in which the statement is made that ERG should be used to differentiate "partial" and "complete" vein occlusion 109.

Green 1981 A pathological study of 39 eyes, 4 atypical cases examined in the acute stage without the presence of rubeosis iridis. He claims to detect thrombosis in the vein or endothelial proliferation 80.

Kohner 1974 In a controlled study, uses streptokinase in patients with CRVO but although a beneficial effect is detected for the recovery of vision, in three patients vitreous haemorrhage ensues a few days after treatment. The conclusion is drawn that the agent should not be used 137.

Laatikainen 1977 A controlled study of panretinal photocoagulation shows a beneficial effect in reducing the frequency of rubeosis iridis but does not increase visual recovery 151.

Ring 1976; Trope 1983. In controlled studies detect raised whole blood viscosity in acute and chronic CRVO with ischaemic cases particularly affected 227, 278.

Hayreh 1978 In experiments on monkeys, he attempts to produce the picture of CRVO by occluding the central retinal artery and or vein. He states that the closest retinal appearance is produced by temporary occlusion of the artery 108.

Fujino 1969 Produces the retinal appearance of CRVO by injecting neoprene into the central retinal vein at the optic nerve head 66.

tery. Study of these circulations is therefore required to determine their contribution to the pathogenesis of CRVO.

8.3 EPIDEMIOLOGY

CRVO is the commonest vascular disorder to affect the retina after diabetic retinopathy, occurring bilaterally in 6-16%^{50,215,222,239}. Some investigators have claimed an increased incidence in males²⁰⁰ whilst others have found no difference for the sexes¹⁸⁹. Although predominantly a condition which affects the middle aged and elderly (90% of patients are aged more than 50 years old⁹², younger patients with CRVO have been described^{41,59,65,222,291} more often males than females⁵⁹. Racial differences have been alluded to by Dodson and Kritzinger (1985) who have observed a low incidence of CRVO in Asians and West Indians⁴¹. In their study of 221 patients with CRVO only 14 were from these races despite 14% of the population in the geographical area belonging to these groups. Similarly in patients under the age of 50 years old a low incidence of races other than Caucasian was detected in a study of a highly selective cohort of patients⁵⁹.

8.4 CLASSIFICATION

Classification aids the efficient clinical management of CRVO by allowing a planned treatment and follow up strategy, however there is disagreement concerning the terminology that should be used. Hayreh has coined the phrases "Venous Stasis Retinopathy" ¹⁰⁰ for the milder type of the disease and "Haemorrhagic Retinopathy" for the more severely affected eyes. The terms "ischaemic" and "non-ischaemic" CRVO have similarly been employed ⁶⁹ and "indeterminate" has been used for those cases which do not fit easily into the previous categories ¹⁷⁶. Finally Gass (1987) has described "impending, mild, moderate and severe" CRVO ⁶⁹. Walsh et al (1977) further classified a mixed group of retinal vein occlusions into primary retinal vein occlusion when there was no systemic disease and secondary retinal vein occlusion in which systemic disease was present ²⁹⁰.

In most circumstances "venous stasis retinopathy" is synonymous with "non-ischaemic" CRVO and "haemorrhagic retinopathy" is synonymous with "ischaemic" CRVO. In the studies described the terms "non-ischaemic" and "ischaemic" CRVO are employed as it is believed that these are less misleading than Hayreh's nomenclature. "Venous stasis retinopathy" may be confused with the stasis retinopathy from carotid artery disease for which the same name has been used ¹²⁷ and "Haemorrhagic

retinopathy" leads the clinician to believe that extensive retinal haemorrhages must be present but this is not always so.

Classification is primarily performed by examining fundus fluorescein angiograms for the presence of retinal capillary non perfusion. When present a case is deemed to be ischaemic with between 22% ¹⁰¹ and 36% ²²² of cases being so classified. Cases of CRVO examined in the acute phase may be mistakenly classified as non-ischaemic because capillary nonperfusion may not be fully developed until three months after onset of occlusion ^{146,177,254}. This explains some of the high "conversion" rates (9-20%) from non-ischaemic to ischaemic CRVO that have been reported in some studies ^{100,196,222,307}.

8.5AETIOLOGY

The condition is associated with common systemic vascular disorders such as hypertension and diabetes (tables 8.3 and 8.4). Abnormal glucose tolerance tests, increased plasma levels of gammaglobulins, triglyceride and cholesterol may be found ^{3,47,238}. CRVO shares many aetiological factors with arterio-sclerotic disease and, indeed, systemic ischaemic disease is found frequently in these patients ^{3,50,142}. However, dissimilarities with arterio-sclerosis exist,

Table 8.3

Prevalence of Systemic Abnormalities in CRVO.

Hypertension. 38-61% of patients 3,37,138,189

Diabetes. 13-15% 3,138.

Abnormal glucose tolerance test.

34% of 79 patients with retinal vein occlusion,
64 with CRVO¹⁸⁹ and 17.5% in another study of
40 patients with CRVO⁴⁰.

Increased plasma gammaglobulin.

28%, increased IgA levels in 17%¹⁸⁹.

Cryofibrinogenemia. 12%¹⁸⁹.

**Increased plasma lipids (hypercholesterolemia or
hypertriglyceridemia)** 32-57%^{40,138,189}.

Arteriosclerosis. 21% of 56 patients⁴⁹.

Increased mean plasma C reactive protein.

A group of 37 hypertensive patients with cen-
tral retinal vein occlusion⁴⁴ compared to
49 normotensive patients with CRVO.

Increased Plasma antiphospholipid antibodies.

Particularly lupus anticoagulant, elevated in
isolated cases of central retinal vein occlu-
sion^{133,219,295}.

Table 8.4

SYSTEMIC RISK FACTORS (%)					
n	Diabetes Mellitus	High Blood Pressure	High Cholesterol	ESR	Arterio-Sclerosis
Dodson 1982	40				
40	15	37.4	22.5	-	-
Kohner 1983	138	not all tests were performed on all patients.			
191	18.2	43.9	30.4	45.5	-
Appiah 1989 ³					
117	13.7	47	7.8	23	22
Cole 1989	37				
47	-	61.7	28.8	-	-
Elman 1990	50				
160	13.1	45	-	-	58
Kotval 1990	142				
87	28.0	67			11

Table 8.4 The percentage of patients with CRVO in whom various systemic disorders have been found.

eg., a significant correlation with cigarette smoking has yet to be found. Ellis et al (1964) found that 51% of vein occlusion patients smoked as compared with 40% of controls, a result which was not found to be significantly different ⁴⁹. The number of patients in this study (56 patients with CRVO) may have been too small to show significance for this difference but it is of interest that all 28 patients in the same study with central retinal artery occlusion were smokers. An increase in mortality is expected in patients suffering arterial occlusion but this has not been reliably found in CRVO ^{47,48,50,183}. Furthermore it is uncertain whether an increase in cardio-vascular or cerebro-vascular mishaps affects these patients. Priluck et al (1980) studied the long term follow-up of 42 young patients under 40 years old with vein occlusion and showed a 12% mortality at a mean 15 years follow up but provided no comparison with a matched population sample ²¹⁸. If a comparison is made with arterial occlusion of the ocular vasculature then differences in aetiology are again found. Central retinal artery occlusion is associated with an increased incidence of carotid artery disease but no such an association has been found for CRVO ²¹². Reduced mean optic disc area, a risk factor for occlusion of the posterior ciliary arteries, has also not been found in eyes with CRVO ^{30,182,263}.

A number of investigators have argued for an inflammatory aetiology for the disease. In one study, evidence of inflammation was found in 48% of 29 postmortem eyes, either in the thrombus, the venular wall or the perivenular area ⁸⁰. CRVO may complicate systemic and ocular inflammatory diseases (table 8.5) and raised plasma C reactive protein may indicate an inflammatory aetiology ⁴⁴.

Primary open angle glaucoma or ocular hypertension has been detected in 4% to 43% of patients with CRVO ^{3,37,224,260,283}. Furthermore, tonography has revealed a reduced aqueous outflow facility in 42% of 71 patients in one study of patients with CRVO ²⁸³.

Hitchings and Spaeth (1976) looked for evidence of previous CRVO or hemiretinal vein occlusion (HRVO), ie., the presence of disc collateral vessels or arteriovenous shunts in patients attending a glaucoma service, and detected an prevalence of 4% ¹¹⁴. CRVO causes an initial drop in intraocular pressure which recovers within a few weeks ^{106,283} but even so an increased mean intraocular pressure was found by Frucht (1985) in 24 patients compared to controls ⁶⁴.

One study has suggested that the presence of open angle glaucoma signifies a poorer outcome from CRVO for the development of iris neovascularisation and visual recovery ²⁸³. However, the group of patients with glaucoma in this study were older than the other pa-

Table 8.5
Case Associations with Inflammatory Disease.

Moyamoya disease 255.

Systemic lupus erythematosus 153

Tuberculosis 61

Acute multifocal placoid pigment epitheliopathy 32

Optic neuritis 47

Aids, 3 patients 59,271

Table 8.5. The diseases involving the immune system
which have been associated with CRVO.

tients which may have affected their prognosis. Dryden (1965) in an examination of postmortem eyes with CRVO found histological evidence of open angle glaucoma in 32% of his 31 cases ⁴⁶. Unfortunately, he does not give the reason for enucleation nor what the criteria for histopathological diagnosis of CRVO were. Large rises in intraocular pressure with changes in posture in patients with CRVO ^{181,298} may reflect the increased incidence of open angle glaucoma which itself causes an increase in postural intraocular pressure variations ²⁷⁶.

The high incidence of raised intraocular pressure has led to the belief amongst some investigators that CRVO possesses a different aetiology to branch retinal vein occlusion in which only 6% to 13% of patients have raised intraocular pressure ^{3,49,64}. In addition, hypermetropia and high blood pressure are commoner in cases of branch retinal vein occlusion whereas raised erythrocyte sedimentation rate is commoner in CRVO ³. The role of intraocular pressure in the aetiology of central retinal vein occlusion has recently been questioned ²²⁵ because a similar incidence of underlying medical conditions has been reported in patients with and without raised intraocular pressure ³⁷. In the same study recurrent CRVO was as common whether intraocular pressure was raised or not. Aetiological factors have also been investigated in young patients with CRVO (table 8.6) ⁵⁸. Walters and

Table 8.6
Young Patients.

Quinlan 1990 Retrospective study of 24 patients less than 50 years of age ²²².

42% Hypertension
13% Collagen vascular disorders

Dodson 1985 40 patients less than 50 years ⁴¹.

35% Hyperlipidemia
60% Medical conditions check

Fong 1991 Selective cohort of 103 patients with CRVO under the age of 50 years (details of these patients were primarily obtained by mailing questionnaires to retinal specialists) ⁵⁹.

25% Hypertension
6.8% Primary open angle glaucoma
6% Hyperlipidemia
6% Heart disease.

Walters 1990 Retrospective study of 17 patients under 40 years of age (but with a large portion of missing data) ²⁹¹.

No evidence of an inflammatory
actiology was detected.

Table 8.6 The findings of studies examining CRVO in younger patients.

Spalton (1990), in a retrospective study of 40 patients less than 40 years of age, reported good general health and also a good visual prognosis ²⁹¹. Most of their patients suffered from non-ischaemic CRVO. Another group of 7 patients aged less than 45 years with ischaemic CRVO frequently had systemic diseases and a poor visual outcome ⁶⁵. Platelet coagulant hyperactivity, associated with mitral valve prolapse has been found in 4 out of 15 young patients ⁷³. Chew looked at a group of 7 young patients less than 36 years old and found that there were diurnal variations in intraocular pressure of 8.8 mmHg in the affected eye with CRVO and 9.3 mmHg in the fellow eye compared to a diurnal fluctuation of 3.7 mmHg in normal controls ³³.

8.6 PATHOGENESIS

It is postulated that raised intraocular pressure causes external compression of the central retinal vein as it passes through the lamina cribrosa resulting in turbulent blood flow distal to the constriction and subsequent thrombus formation. The thrombus has been difficult to detect histologically, partly because pathological studies have been performed on cases of rubeotic glaucoma in which the veins are often recanalised ¹³⁵. Klein found damaged endothelium and proliferation of endothelial cells in enucleated eyes

of such patients, sometimes with the presence of intramural thrombus ¹³⁵. It was not until Green et al (1991) examined 29 affected eyes and found that thrombi were found in the venous lumen of a few cases of non-rubeotic eyes ⁸⁰. This small group of 4 patients was examined within 24 hours of occlusion and found to have thrombus in the vein close to the lamina cribrosa. None of these cases can be described however as typical cases of CRVO: one patient aged eight months had Reye's syndrome, one patient had massive intracranial haemorrhage and papilloedema, another had acute myelogenous leukaemia and the remaining patient had died of myocardial infarction with no clinical evidence of CRVO. The rubeotic cases in the same study showed recanalised thrombus or vascular endothelial proliferation. Thrombus was situated at the lamina cribrosa with extension posteriorly in 24 eyes and anteriorly in 5 eyes. Multiple small venous channels were often present in those with a short duration from onset of the occlusion whereas those of long duration showed the presence of a single venous channel.

Hayreh et al (1978) amongst others have argued that central retinal artery occlusion is an essential component in the pathogenesis of CRVO believing that the haemorrhagic form of CRVO is probably due to a combination of arterial and venous occlusion. Evidence for the hypothesis is provided by experimental studies on monkeys in which occlusion of the central retinal

vein and temporary occlusion of the central retinal artery at their emergence from the optic nerve produced a clinical appearance in the retina with some similarities to CRVO whereas occlusion of the central retinal vein alone at this site did not, (table 8.7) ¹⁰⁸. This experimental model, however, produced features which are not usually seen in CRVO in humans (eg., internal limiting membrane detachment and rapid resolution of retinal changes). In addition, neovascularisation which is a primary complication of CRVO was not produced.

Such experimental blockage of the central retinal vein distal to the optic nerve head does not take into account collateral venous channels around the optic nerve and may explain why there has been failure of production of CRVO by blockage at this site. Fujino (1969) using the owl monkey injected neoprene into the vein to produce occlusion at the optic nerve head ⁶⁶. In this experiment he was able to produce a haemorrhagic retinopathy with evidence of back pressure on the arterial circulation. In comparison a group of monkeys with occlusion of the central retinal vein at the emergence from the optic nerve in the orbit produced only a temporary and reversible increase in retinal venous congestion.

Experimental models can be criticised particularly, because the animal models used are always younger

Table 8.7

EXPERIMENTAL CRVO
Hayreh 1978 108

Central Retinal Vessel Occluded	Retinal Features
Vein	Ilm detachment, dilated engorged veins, mild retinal haemorrhaging, optic disc leakage.
Vein and Artery (Permanent)	Ilm detachment, mild retinal haemorrhaging, optic disc leakage, capillary closure.
Vein and Artery (Moderate Duration)	Ilm detachment, dilated engorged veins, mild retinal haemorrhag- ing.
Vein and Artery (Short Duration)	Ilm detachment, dilated engorged veins, marked retinal haemorrhaging, optic disc leakage, capillary closure.

Fujino 1969 66

Vein at Optic Nerve Head	Mild retinal haemorrhaging, sometimes venous distension, normal arterial filling on fluorescein angiography.
Vein at Emergence from Optic Nerve	Marked retinal haemorrhaging, engorged veins, delayed arterial filling, histologically capillary necrosis.

Table 8.7. The observations from experimental studies
of central retinal vessel occlusion in monkeys.

(relatively) than the usual age of human patients with CRVO and therefore their vasculatures are dissimilar to the aged blood vessels in most patients. Our understanding of the arterial involvement may be improved by in vivo investigation of the arterial and venous circulation in humans with techniques such as colour Doppler ultrasound by allowing the examination of the velocity of blood flow in the central retinal artery and vein simultaneously.

Jorrizo et al (1987) argued that prolonged arteriovenous dye transit times on fluorescein angiography provide evidence of arterial occlusion ¹²⁴ but these could be due to back pressure on the arterial circulation from the congested veins. Ophthalmodynamometry has also been used to try to illustrate the presence of arterial insufficiency in CRVO ²⁵⁸.

Patients with an appearance similar to that of CRVO have been described with carotidocavernous sinus fistula ^{25,216,265}. These cases provide evidence for increased back pressure in the venous circulation without arterial occlusion. One case described by Suzuki showed a venous stasis retinopathy appearance which progressed to haemorrhagic retinopathy suggesting the presence of ischaemia ²⁶⁵. Although the retinal changes seen in these cases are probably the result of increased venous pressure, secondary central retinal arterial occlusion or "steal" from the arterial circulation may also be present.

McLeod (1976) investigated eleven patients with combined occlusion of the cilio-retinal artery and central retinal vein. Retinal haemorrhages were less prominent in the area of the arterial infarct than in the surrounding retina ¹⁹¹ which is contrary to the expectations of Hayreh which suggest that haemorrhage should have been present within the area of retina supplied by the occluded artery ¹⁹⁰. A lower perfusion pressure in the cilio-retinal artery compared with the central retinal artery may explain why these arteries become blocked in vein occlusion, possibly by back pressure from the venous circulation. Video fluorescein angiography has shown that pulsations are present in these arteries ²⁴⁶ suggesting that there is back pressure without occlusion.

Green et al (1981) demonstrated arterial occlusion in 24% of postmortem eyes ⁸⁰ but the majority of these eyes were rubeotic and may therefore have suffered arterial occlusion secondarily to raised intra-ocular pressure. The CRVO picture has also been described in Moyamoya disease which is considered to be a disease of intracranial arteries ²⁵⁵.

The relative roles of occlusion of the central retinal artery and vein in the production of the appearance of CRVO is therefore uncertain. Indeed the mechanism of the occlusion is still open to investigation.

8.7 CLINICAL INVESTIGATION OF CRVO

The primary roles of investigation of CRVO in the clinical setting have been to identify underlying systemic and ocular conditions which require treatment, and to classify the vein occlusion thereby determining the risk of neovascular glaucoma and the prognosis for visual function. A number of tests has been used for this including clinical parameters such as visual acuity, ophthalmoscopy, relative afferent pupillary defect, visual field assessment and investigations such as electroretinography and fluorescein angiography. Hayreh et al (1990) in an extensive prospective study compared functional tests such as visual acuity, visual field, relative afferent pupillary defect and electroretinography against "morphological" tests of ophthalmoscopy and fluorescein angiography¹⁰⁴. Overall, they found that functional tests were better measures of ischaemia according to his classification system. There is, however, a reservation in the methodology for this study. Their parameters for classifying a patient as having ischaemic central retinal vein occlusion involved the following: presence of ocular neovascularisation or the presence of extensive capillary non-perfusion on fluorescein angiography or three of the following four findings; (i) relative afferent pupillary defect of more than or equal to 1.2 log units; (ii) the presence of 10 or more

cotton wool spots; (iii) a visual acuity of count fingers at 1-2 feet; or (iv) a visual field with sensitivity of less than or equal to V4e on Goldmann testing. Therefore the tests in their classification system were the same tests which they intended to assess. Despite this, some interesting results were found, for example, some investigations were dependent on the time of examination, ie., how long after the onset of the occlusion, such as fluorescein angiography and ophthalmoscopy whereas other tests were less duration dependent such as relative afferent pupillary defect and ERG. Visual field assessment and visual acuity appeared not to be duration dependent until after one year. ERG was not used in their initial classification and therefore data for this test were probably the most accurate showing it to be a good predictor of ischaemia.

8.7.1 CLINICAL PARAMETERS

Visual acuity, a simple, straightforward and readily available test, shows some predictive power for the development of neovascular glaucoma ^{254,290} but its value is reduced because the presence of cystoid macular oedema a common complication of CRVO reduces visual acuity in many non-ischaemic cases. A quantitative assessment of relative afferent pupillary

defect (RAPD) using neutral density filters ²⁷³ has been used to investigate 120 patients with CRVO ²⁵⁰. A pupillary defect of at least 1.2 log units was detected in all 11 patients who developed new vessel formation in this study. Also 90% of the patients classified as ischaemic had a RAPD of at least 1.2 log units, whereas none of the nonischaemic patients did. The test is particularly useful because the pupillary defect does not appear to change with the duration after onset of the central retinal vein occlusion but will increase in an eye that evolves into an ischaemic pattern.

8.7.2 FLUORESCEIN ANGIOGRAPHY

A number of parameters on fluorescein angiography have been used in the classification of CRVO, the most important of these being retinal capillary non-perfusion which has been shown repeatedly to predict the development of rubeosis (figure 8.3) 149,150,175,177. Unfortunately, the identification and quantification of this sign is subjective and difficult to standardise. An assessment of its extent may be improved by 60 degrees wide angle photography and objectivity introduced by image analysis ¹⁷⁷. Serial fluorescein angiograms have shown that capillary closure increases with time and so early examination may underestimate the final extent of the retinal ischaemia ^{177,254}. This progressive loss of capil-

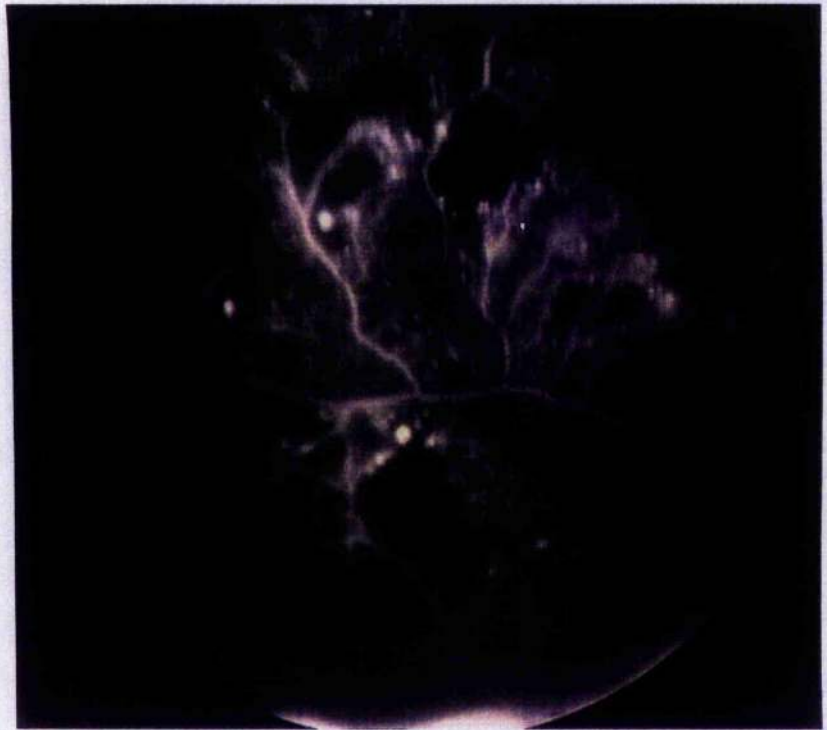


Figure 8.3. A fundus fluorescein angiograph of a patient with CRVO showing capillary nonperfusion (drop out).

laries with time has also been demonstrated histologically in experiments using monkeys ¹⁰⁸.

Other fluorescein angiographic signs have been investigated such as the condition of the perifoveal capillary arcade, an intact arcade providing a good indicator for recovery of visual acuity. Cystoid macular oedema usually occurs if there are breaks in the continuity of this arcade but this complication may still occur with an intact arcade if severe venous leakage is present ¹⁵⁰. Sinclair (1979) found that 84% of patients with cystoid macular oedema achieve visual acuity of 6/7.5 or better if their perifoveal arcade is intact ²⁵⁴.

Studies of the time required for transit of fluorescein dye from the arterial retinal circulation to the venous have revealed varied results. Zegarra et al (1974) found that there were equal arteriovenous transit times in patients with ischaemic and non-ischaemic CRVO ³⁰⁷. Whereas, Laatikainen (1976) using macular transit time in patients examined less than three months after onset, found that delay was more often present in those who developed neovascular glaucoma ¹⁵⁰.

Widespread retinal haemorrhages may severely hamper detailed examination of the retinal vasculature by fluorescein angiography. Hayreh et al (1990) determined that one third of fluorescein angiograms (from 140 eyes of 128 patients) had been inadequately

assessed because of the presence of such factors as retinal haemorrhage and opacities of the media ¹⁰⁴. Sinclair and Gragoudas (1979) found that 11% of the fluorescein angiograms of 57 patients did not allow adequate assessment of the perifoveal arcade due to retinal haemorrhages ²⁵⁴. In addition, because of the largely subjective nature of fluorescein angiography, there is considerable intra-examiner disagreement in its assessment. Welch (1987) found a surprisingly high intra-observer error (from 8 observers) with only 67.8% agreement between two assessments of 26 angiograms by the same observer ²⁹⁵. Using forced choice methodology only 35% of examiners made a correct classification of ischaemia on one observation. Even so, fluorescein angiography remains the most frequently quoted indicator of ischaemia.

8.7.3 ELECTRORETINOGRAPHY (ERG)

A number of investigators have found that ERG is a useful test for detecting ischaemia, (table 8.8) 22,104,105,123,126,201,241,290. The predictive potential for the detection of patients who develop iris neovascularisation is often superior to fluorescein angiography but the most efficient testing strategy or portion of the ERG waveform to examine has yet to be determined (figure 8.4).

A common abnormality of the ERG in CRVO is a reduction

Studies of Electroretinography.

Sabates 1983 strobe light 45 patients. 241

He determined that the best measure of the risk of neovascular glaucoma was the b/a ratio. Mean b/a ratio was 1.67 (all were above 1.0) for 27 patients with venous stasis retinopathy and 0.70 for the 6 patients with haemorrhagic retinopathy (all less than or equal to 0.76). All 6 patients who developed neovascular glaucoma had ratios of less than 1.0 (mean 0.94). A paradoxical increase in the b wave was seen in some of the patients with venous stasis retinopathy, an effect which can also be seen in patients with hypertension or those using vasodilator drugs. Although the b/a ratio could be used to predict the development of neovascular glaucoms it did not predict the final visual acuity result.

Kaye 1988 30 patients 126 Ganzfield bowl, a gold foil electrode.

26 patients with non-ischaemic CRVO and 4 with indeterminate CRVO, 7 patients went on to develop iris neovascularisation at 6 months. The best predictor of this complication was mean b wave implicit time (a time of $>47.17\text{ms}$ or an inter eye difference of $>7.39\text{ms}$ predicted iris neovascularisation formation), followed by b/a ratio and then b wave amplitude. 95% confidence limits of mean b wave implicit time for eyes which subsequently developed rubeosis did not overlap with those for eyes unaffected by rubeosis. Results for b/a ratio showed overlap at 99% confidence limits compared to nonrubeotic eyes and overlap at 95% confidence limits for the fellow eye comparison.

Johnson 1988 15 patients with CRVO for flash and flicker ERG with a hemisphere illumination and a Burian Allen bipolar contact lens. 123

7 with current iris neovascularisation and 2 who subsequently developed iris neovascularisation. She used the Naka-Rushton physiological compression formula to produce an analysis of flash waveforms. In this study a computerised forced choice analysis was performed to assess the discriminant value (presented as a percentage) of each of the parameters for the prediction of neovascularisation. The order of values was logK 88%, Rmax 82%, flicker implicit times 61% and b/a ratio 27%. This was compared with the forced choice analysis of the detection rate by six retinal specialists studying fluorescein angiograms of patients with iris neovascularisation in which a detection rate of only 36% was obtained.

Hayreh 1989 149 eyes of 128 105 Gass photostimulator and hemisphere bowl with a contact lens electrode.

He compared the results of his patients classified as either ischaemic or nonischaemic. Combining data for the photopic and scotopic waveforms determined that the b wave amplitude had the best sensitivity (80-90%) and specificity (70-80%), followed by b/a ratio (sensitivity 60-70% and specificity 70%), then a wave amplitude (sensitivity 60-70% and specificity 60-70%) and finally implicit times (sensitivity 30-55% and specificity 70-80%). Further analysis of the patients with ischaemic CRVO showed that ERG was unable to predict the occurrence of neovascularisation in these cases.

Breton 1989 21 patients 22 Ganzfield bowl and disposable unipolar contact lenses.

Multiple discriminant analysis of a number of parameters including those from the Naka-Rushton equation. A 14% false positive rate for the prediction of iris neovascularisation was found using this method.

Morrell 1991 41 patients 201 DTL fibre corneal electrode (and a Gass strobe for flash responses).

Examined pattern ERGs and found that it was significantly reduced in a group of 8 patients who went on to develop rubeosis iridis. In this study, flicker implicit times were the best predictor for the development of rubeosis. Using an inter-eye difference of more than 6 secs as the cut off, a false positive rate of 2% and false negative rate of zero were found. This compared with a false negative rate of 52.5% for fluorescein angiography. The examination strategy employed in this study required 1 to 1.5 hours of time to perform.

Gouras 1992 12 patients 75 using a Burian Allen bipolar contact lens electrode and a Gass strobe fitted to a Ganzfield bowl)

Different wavelengths of light at different levels of light adaption. The cone ERG was delayed but increased in amplitude in comparison to the fellow eye especially for the light adapted eye at long wavelengths of light (red). This effect has been attributed to an inability of the cones in the retina affected by CRVO to reduce their responsiveness to light with increased levels of light adaption.

RIGHT EYE

LEFT EYE

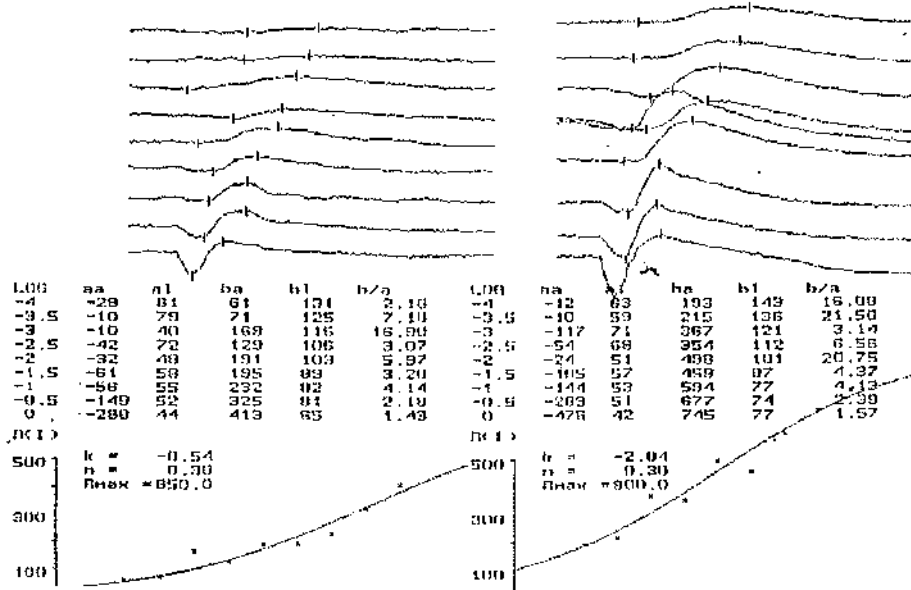


Figure 8.4. The electroretinographic waveforms (scotopic series and Naka Rushton slope) from a patient with CRVO of the right eye.

in the b wave amplitude. This portion of the ERG waveform is produced by the Muller cells in the retina which are damaged by the ischaemia induced by CRVO. The a wave which results from the retinal receptors, is relatively preserved because the outer retinal layers are supplied by the choroidal circulation.

The amplitude of both the a and b waveforms can be reduced from other factors such as medial opacities. In order to reduce the influence of such factors a ratio of the b wave to the a wave is often used. The b/a ratio is small in CRVO because of reduction of the b wave and because the amplitude of the a wave which is normally reduced by destructive interference from the b wave may be increased in CRVO.

Many other measurements are available from the electroretinogram such as a and b wave implicit times or measurements from the physiological compression formula of Naka and Rushton.

Naka-Rushton Formula.

$$R = \frac{R_{max} I^n}{I^n + K^n}$$

R = Amplitude from a wave trough to Bwave peak.
 Rmax = Maximum ERG amplitude
 I = Stimulus intensity
 K = Intensity to reach 1/2 Rmax
 n = Slope of the function

LogK is used as an indicator of the level of light required to obtain a "normal" amplitude and is used as a measure of the loss in sensitivity of the cells.

Rmax is used as a measure of the loss of cell numbers and the slope n is used as a measure of the homogeneity of the retinal sensitivity. The ERG may be used to measure photopic or scotopic responses, colour response or flicker response. Not surprisingly there is much debate as to the most useful parameters to measure in CRVO.

The fellow eye has been used for comparison in many of the studies on ERG in CRVO. Sakue (1989) found that 18 out of his 50 patients had abnormal ERGs in the fellow eye. 15 of these had supernormal ERGs (increased a wave amplitudes) of 2 standard deviations above the normal controls and three had negative ERGs (reduced a/b ratio) ²⁴².

8.8 VISUAL OUTCOME

Non-ischaemic CRVO has a better outcome with less frequent development of neovascular glaucoma and with good recovery of visual acuity ¹⁰⁰. Ischaemic cases have a poor prognosis for the recovery of vision ^{149,222,307}. Zegarra et al (1979), in a prospective study of the natural course of CRVO in 26 eyes of 25 patients, found that the final visual acuity was 3/60 or worse in 87% of the ischaemic group (16 eyes) whereas the non-ischaemic group (10 eyes) had 6/18 vision or better in 80% ³⁰⁷. Quinlan et al (1990) found retrospectively in 168 eyes of 160 patients that

93% of ischaemic CRVO (61 eyes) culminated in a final visual acuity of less than 6/60 as opposed to 50% of non-ischaemic CRVO (107 eyes) ²²². The final vision in young patients with CRVO was 6/60 or worse in 32% and no light perception in 6% in a large selective cohort of patients ⁵⁹.

9.9 NEOVASCULARISATION AND NEOVASCULAR GLAUCOMA

Approximately 21% of cases of CRVO develop rubeosis iridis usually by six or seven months after onset although it can occur as late as 24 months from presentation (table 8.9, figure 8.5) ^{196,254,307}. Neovascular glaucoma has been reported in 8-50% of CRVO ¹⁰⁷, 67-82% of ischaemic CRVO ^{107,176,307} and only 1% of those with non-ischaemic disease ^{107,222,307}. Magargal's "indeterminate" group (1989) which fall in between these other classifications developed neovascular glaucoma in 7% of his 29 cases ¹⁷⁷. New vessels in the posterior segment usually occur in only 5-7% of eyes with CRVO ¹⁰⁷ but have been found in 30% of 61 eyes with ischaemic CRVO in one study ²²². In patients under 50 years of age rubeosis has been described in 19%, neovascular glaucoma in 8%, disc or retinal new vessels in 1% in a study of 103 cases ⁵⁹. Although rubeosis of the iris may occur as late as 24 months after onset ¹⁹⁶ the majority of cases, 71% of 35

Table 8.9

NEOVASCULARISATION						
n	Iris Angle Glaucoma Disc Retina (% of patients)					All
Kruger 1990 145						
Nonischaemic						
283	3	2	1	0	0	3
Ischaemic						
78	58	47	33	5	8	87
Magargal 1981 176						
Nonischaemic						
70	-	-	1	-	-	-
Ischaemic						
45	-	-	60	-	-	-
Priluck 1980 218						
Nonischaemic						
21	-	-	0	0	0	0
Ischaemic						
21	-	-	14	5	-	-
Zegarra 1979 307						
Nonischaemic						
10	-	-	0	0	0	0
Ischaemic						
26	-	-	26	0	0	26
Laatikainen, 1977 148						
Nonischaemic						
11	-	-	8	0	0	-
Ischaemic						
13	-	-	18	45	18	-

Table 8.9. The percentage of patients with ischemic or nonischaemic CRVO who suffer from neovascularisation of the iris, angle, disc and retina, and neovascular glaucoma in various studies.

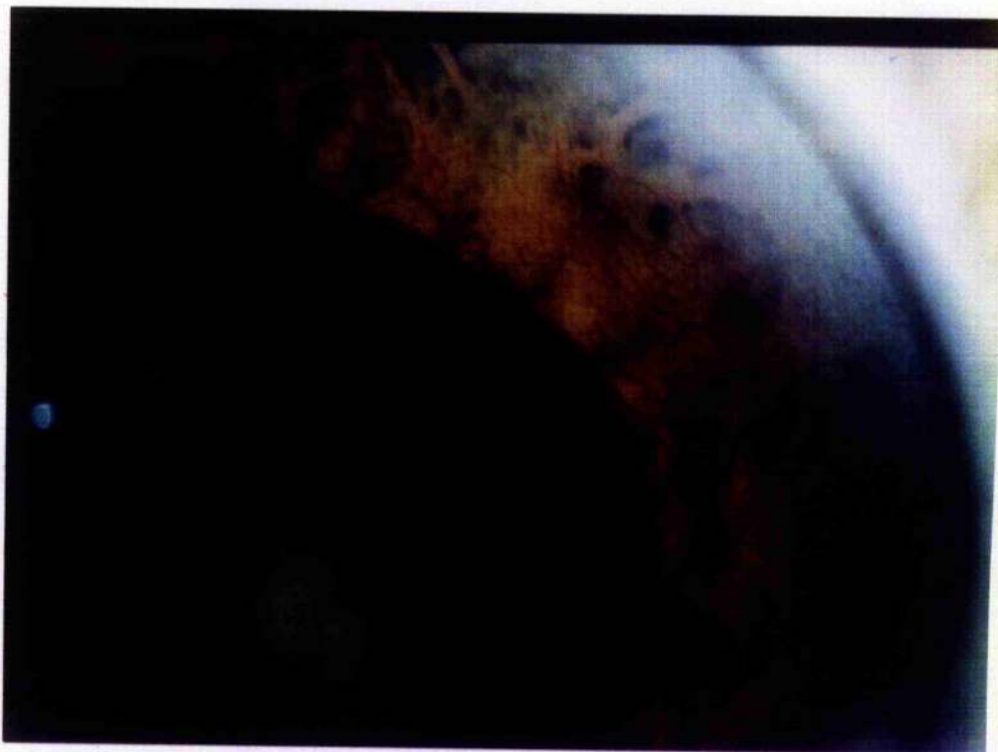


Figure 8.5. Iris neovascularisation is shown in a slit lam
photograph.



Figure 8.6. A fundus photograph of the chorioretinal changes
associated with panretinal photocoagulation is shown.

patients in one study ³⁰⁷, occur within the first six months. The neovascularisation may affect the iris or the anterior chamber angle causing anterior synechiae to appear. These changes can be graded to aid the assessment of therapeutic strategies ³⁰⁷. Magargal (1982) ¹⁷⁷ performed a retrospective study of the natural history of CRVO without treatment which included 42 patients with untreated rubeosis and found that 76% of these patients went blind to no perception of light in the affected eye and 28% developed phthisis bulbi or required enucleation of the eye for pain (none of the cases was treated with panretinal photocoagulation) ¹⁷⁷. Ninety three percent of the patients' eyes which developed iris neovascularisation had more than 50% retinal capillary nonperfusion on microcomputer assessment of fundus fluorescein angiography. In the same paper Magargal also described 22 eyes with ischaemic CRVO treated with panretinal photocoagulation none of which developed iris neovascularisation. Interpreting the results in a different way showed that the treatment of all patients with CRVO on the grounds of 50% capillary drop out would have lead to a significant proportion being treated unnecessarily because, of 200 patients with 50% capillary drop-out or more, only 60% subsequently went on to develop rubeosis. That is 50% capillary drop out had a high sensitivity but a low specificity for the prediction of those patients who would develop iris neovascularisation.

Disc and retinal new vessels occur with central retinal vein occlusion in approximately 5-7% of cases in contrast to the development of new vessels in branch retinal vein occlusion in 23%¹⁰⁷. Whereas, new vessels of the iris appear within the first six months, new vessels of the disc and retina take longer to appear usually one year after the occlusion occurs²⁰². Histological studies demonstrate a lack of viable retinal vascular endothelial cells after CRVO. Theoretically, an angiogenic factor would be unable to act on the retinal vessels themselves, instead it diffuses into the anterior segment and causes new vessels on the iris³¹. Murdoch et al (1991) have suggested that panretinal photocoagulation may convert an ischaemic retina into a partially ischaemic retina and thereby cause the production of new vessels of the disc or the retina²⁰². He described five patients in whom new vessels of the posterior segment appeared after apparently successful treatment of rubeosis iridis by panretinal photocoagulation. May et al (1979) described 6 of 15 patients in whom posterior segment new vessels occurred after panretinal photocoagulation¹⁸⁷ but 6 of 19 untreated patients also developed posterior segment neovascularisation in the same study.

9.10 TREATMENT OF CRVO

The mainstay of treatment of central retinal vein occlusion is panretinal photocoagulation (figure 8.6). Laatikainen et al (1977) in a prospective randomised trial ¹⁵¹ determined that Xenon panretinal photocoagulation reduces the incidence of neovascularisation and cystoid macular oedema but has no effect on visual acuity. These findings have been confirmed by May et al (1979) who found no neovascularisation of the iris or neovascular glaucoma after treatment and who also found no improvement in visual acuity ¹⁸⁷. Others have used panretinal photocoagulation in the treatment of neovascular glaucoma and rubeosis and have been able to show that the neovascularisation can be reversed ^{175,186,202}. Magargal et al (1982) even stated that treatment was always successful unless another ischaemic event was encountered in the eye ¹⁷⁷. May et al (1979) and Murdoch et al (1991) have both demonstrated that neovascularisation of the retina or disc may occur despite panretinal photocoagulation ^{187,202}. Dodson et al (1985) ⁴³ detected an increase in blood pressure, alcohol abuse and lower plasma HDL levels in patients with recurrent central retinal vein occlusion and has claimed that medical treatment of these reduces the recurrence rate of central retinal vein occlusion from 10-15% to 1% ⁴². Anticoagulants and fibrinolytic agent have been tried unsuccessfully to treat the

condition 137,154,282.

Vitrectomy to remove vitreous haemorrhage secondary to retinal neovascularisation did not improve visual acuity significantly in one study ²⁵⁷. In one case of pseudotumour cerebri (complicated by central retinal vein occlusion and increased CSF pressure) a reduction in the severity of the retinal features was observed after optic nerve sheath decompression ⁸⁹.

9 Chapter 9

CENTRAL RETINAL VEIN OCCLUSION, AN INVESTIGATION BY COLOUR DOPPLER IMAGING: BLOOD VELOCITY CHARACTERISTICS AND PREDICTION OF IRIS NEOVASCULARISATION.

9.1 Summary.

The purpose of the studies described in this chapter was to determine pulsatile blood velocities in the orbital vasculature in patients with central retinal vein occlusion (CRVO). The ophthalmic artery, central retinal artery and vein of 80 patients with CRVO were investigated by color Doppler imaging (CDI). The patients were examined by ophthalmoscopy, relative afferent pupillary measurement using crossed polarised filters, fundus fluorescein angiography and electroretinography in order to estimate the degree of retinal ischaemia. Blood flow velocities in the central retinal vein and artery of eyes with CRVO were significantly lower than in fellow eyes and controls. The measurements from the vein were most reduced and in some cases absent in those eyes with "ischaemic" CRVO. Velocities were also reduced in the central retinal artery of the affected eyes but no correlation with "ischaemia" was detected. The risk of iris neovascularisation in patients examined within 3 months of onset of CRVO can be determined from the flow velocities (V_{min} of less than 3.0 cm/sec) with a high degree of predictability (75% sensitivity and 86%

specificity). Blood velocity was reduced in the retinal circulation of patients with CRVO and reduced even further in the "ischaemic" variant of CRVO. The results indicate that noninvasive color Doppler imaging could play a major part in the routine assessment of patients with CRVO within three months of onset.

9.2 Introduction

There are few reported haemodynamic investigations of the central retinal vein occlusion (CRVO) perhaps because optical methods of blood flow measurement are difficult to apply to a retina with extensive haemorrhage 150,246,258,307. The present study examined the ophthalmic artery and central retinal artery and vein in 80 patients with CRVO and involved a comparison of the results with the control population described in Chapter 3.

The risk of the development of intraocular neovascularisation requires the classification of eyes affected by CRVO into ischaemic or nonischaemic variants 69,101. Although a number of tests has been applied none has been satisfactory on its own and often a combination of investigations has been required 104,150,250. The results of colour Doppler imaging were therefore analysed to determine whether this investigation could be used to detect eyes at risk of neovascularisation.

9.3 Patients and Methods.

Patients and Classification.

85 eyes with central retinal vein occlusion of 80 patients were examined. The results from 75 unaffected fellow eyes and the control population of 95 ophthalmologically healthy volunteers (see chapter 3) were used for comparison with the disease group. Patients' eyes were excluded if there was evidence of previous ocular surgery or if the intraocular pressure was greater than 30 mmHg and only the most recently affected eye of patients with bilateral CRVO was included in statistical analysis.

To allow a classification of retinal ischaemia the patients were also examined by ophthalmoscopy, relative afferent pupillary defect (RAPD) measurement, fundus fluorescein angiography and electroretinography. The RAPD was measured by attenuating the light received in the unaffected eye from a binocular indirect ophthalmoscope headlamp by rotating cross polarised filters (Stereo Optical) in an adaption of a previously described technique ²³⁷. When the RAPD was neutralised the angle between polarisers was recorded as a measure of the severity of the defect. Electroretinography was performed using a Ganzfeld dome and disposable contact lens electrodes. Fluorescein angiograms were interpreted by observers masked to the other clinical

and investigative results. Seventeen patients were examined by photographic fundus fluorescein angiography using a wide angle Canon Fundus camera and 55 patients by videoangiography using a Rodenstock scanning laser ophthalmoscope (described in chapter 10). Angiograms were not performed in one patient because of a risk of an allergic reaction, in one who refused and in four because of a prolonged interval since the onset of the CRVO. Videoangiography was interpreted by three ophthalmologists with experience of this technique and classification applied when at least two of the observers were in agreement. Three categories "nonischaemic", "partially ischaemic" and "ischaemic", were used according to the criteria shown in table 9.1. The patients were re-examined at a minimum of 12 months after the onset of the CRVO. Four patients were excluded because of a duration from onset of less than 1 year and three patients were lost to follow up. Iris neovascularisation was detected on slit lamp biomicroscopy and gonioscopy, and the presence of retinal neovascularisation noted.

Color Doppler ultrasound

An Acuson 128 with a 7.5 MHz probe was used to obtain velocimetry measurements as has been described in chapter 3. Velocity measurements from the posterior ciliary arteries were not made because the reproduc-

Table 9.1

Classification of CRVO.

Ischaemic.

1. Fluorescein angiographic evidence of severe capillary dropout (>10 disc diameters)
OR if the fluorescein is unassessable:
2. Presence of iris neovascularisation.
OR
3. At least two of the following
 1. Reduction in the B/A wave amplitude of the ERG.
 2. RAPD of at least 20 degrees (cross polarisers)
 3. Visual acuity less than 6/60.

Nonischaemic.

1. No capillary drop out on fluorescein angiography.
AND
2. Absence of iris neovascularisation.
AND
3. Normal ERG.
and
4. RAPD of less than 20 degrees.

Partially ischaemic.

Any case which cannot be fitted into the above categories.

ibility experiments had shown high coefficients of repeated measures for the velocity results. Informed consent was obtained from all volunteers and patients before examination which was performed by an examiner who was masked to the clinical results of the patient.

Statistical Analysis.

Data were stored on a database and analysed using statistical software on an IBM personal computer. Only those patients with unilateral disease and healthy fellow eyes were used in the comparison of CRVO with fellow eyes. Mann Whitney U test, Spearman Rank correlation and Wilcoxon matched pairs test were applied where appropriate. Two methods were employed to overcome the disparity between the age of the controls and the patients. Firstly the results from these two groups were analysed using analysis of covariance with the covariant "age" to allow an age adjusted comparison (the mean age of the controls was 46.6 years, SD 18.2). Secondly, thirty six patients were age and sex matched to 36 patients for a case controlled comparison. Receiver operator characteristic curves were employed to determine a cut-off value for Doppler velocities for the determination of the risk of iris neovascularisation.

9.4 Results.

The mean age of the patients was 67.2 years (SD 13.5, range 27-87), 41 males and 39 females. Eighty five eyes (37 right eyes, 48 left and 5 bilateral), of 80 patients were examined. A flow diagram of the patients used for each part of the analyses is shown in figure 9.1. Three patients were excluded with raised intraocular pressures above 30 mmHg at presentation. The mean duration from the onset of the CRVO to the date of examination was 4.1 months (SD 4.8), median 2 months, range 1 week to 2 years. In the case controlled comparison the mean age of the patients and controls was 60.0 years (SD 15.7 years, range 25 to 85 years) with male female ratio in each group of 1:1.

Central retinal vein occlusion.

Table 9.2 shows the velocity results from the eyes with CRVO, their fellow unaffected eyes and the control population. Figures 9.2, 9.3 and 9.4 show that the majority of eyes with CRVO had lower velocities and venous pulsatility indices in the central retinal vein than their fellow unaffected eyes (65% of the values of V_{max} , 55% of V_{min} and 59% of venous pulsatility indices in CRVO eyes were lower than in the fellow unaffected eyes). Comparison of the eyes with CRVO with fellow eyes and the control population showed significantly lower velocities in the central retinal artery and vein

Figure 9.1

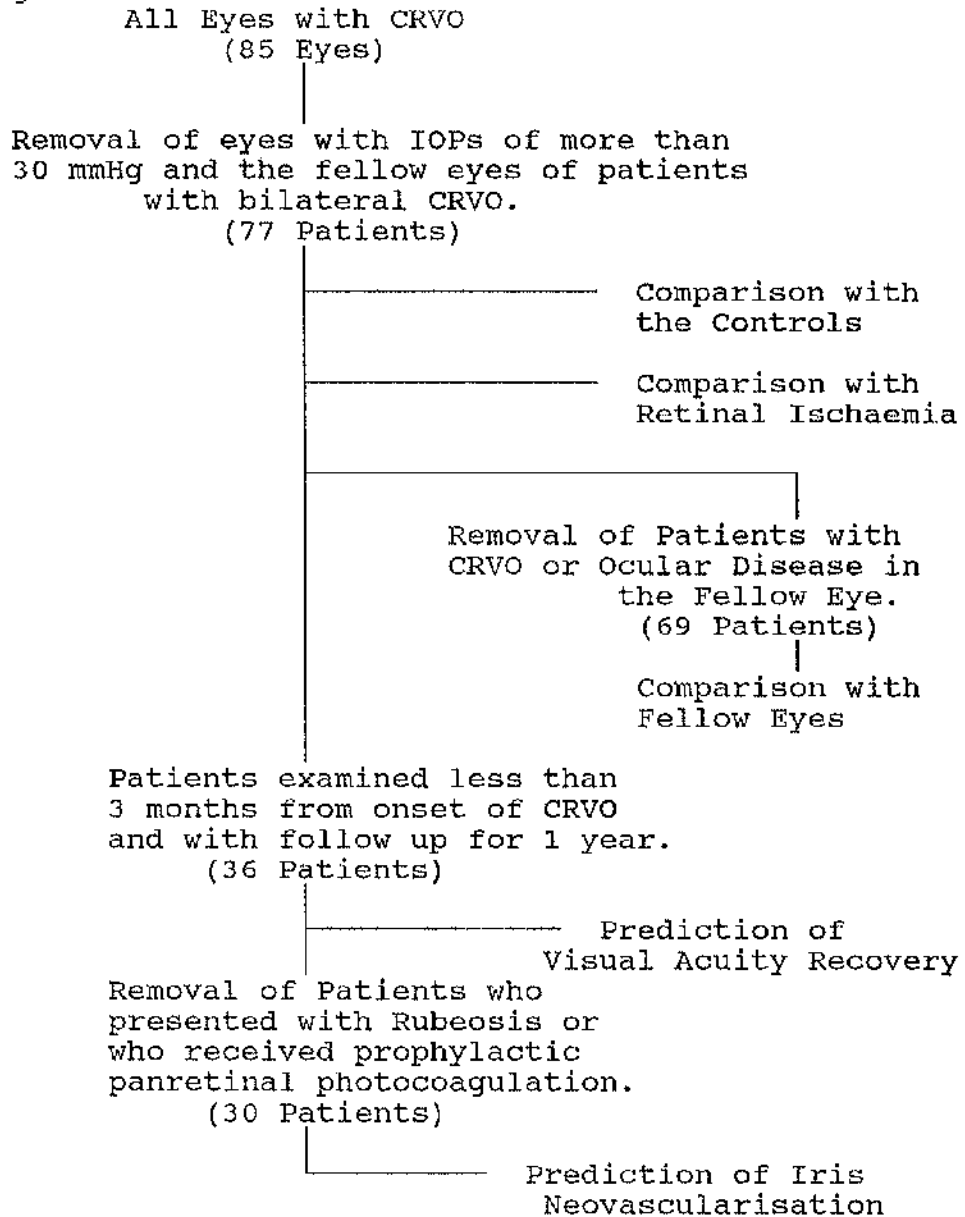


Figure 9.1. A flow diagram showing the manipulation of the data during the analyses (number of eyes remaining after each step).

Table 9.2.

	Ophthalmic Artery		Central Retinal Artery		Central Retinal Vein	
	PSV	EDV	PSV	EDV	Vmax	Vmin
	(mean and SD, cm/sec)					
CRVOS (80)	36.8	8.3	9.1	2.3	4.3	3.1
	10.9	4.1	3.2	1.6	2.1	1.6
FELLOW EYES (72)	36.8	8.4	10.5@	2.9*	6.3*	4.1*
	10.0	4.1	3.1	1.1	2.1	1.1
CONTROLS (95)	35.1	8.6	10.2#	3.1+	5.8*	3.8+
	11.2	3.9	2.9	1.1	1.5	0.9

Table 9.2. The velocimetry results from the eyes with central retinal vein occlusion (CRVO), their contralateral healthy eyes (fellow eyes) and controls. There are significant reductions in the velocities in the central retinal vein and to a lesser extent in the central retinal artery of those eyes with CRVO compared to the fellow eyes and the controls (* $p < 0.0001$, @ $p < 0.001$, # $p < 0.01$, + $p < 0.03$). No differences were found between the velocities in the ophthalmic artery or between the comparison of the fellow eyes with controls.

Retinal Vein Vmax

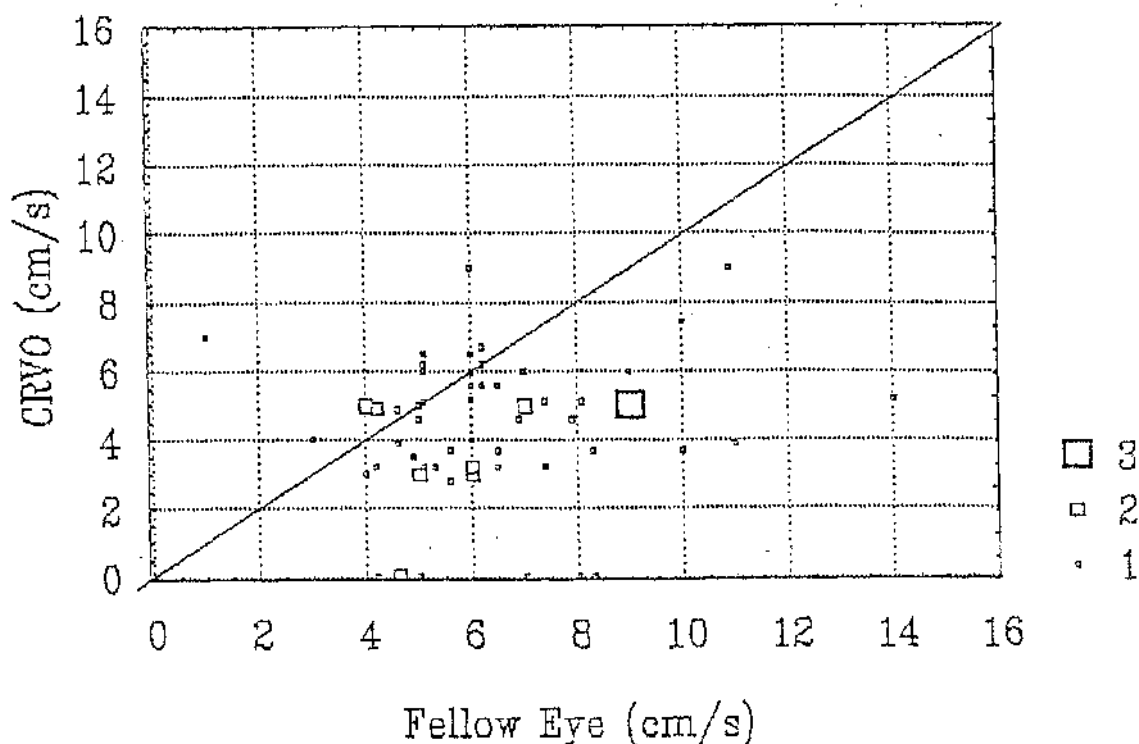


Figure 9.2. A scattergram of Vmax in the central retinal vein of the eyes with CRVO and their unaffected fellow eyes. The points are predominantly scattered below the line showing that for the majority of patients the velocities were lower in the affected eyes than the unaffected eyes. The key shows the number of cases represented by each point, eg., the large circle represents three cases at that point.

Retinal Vein Vmin

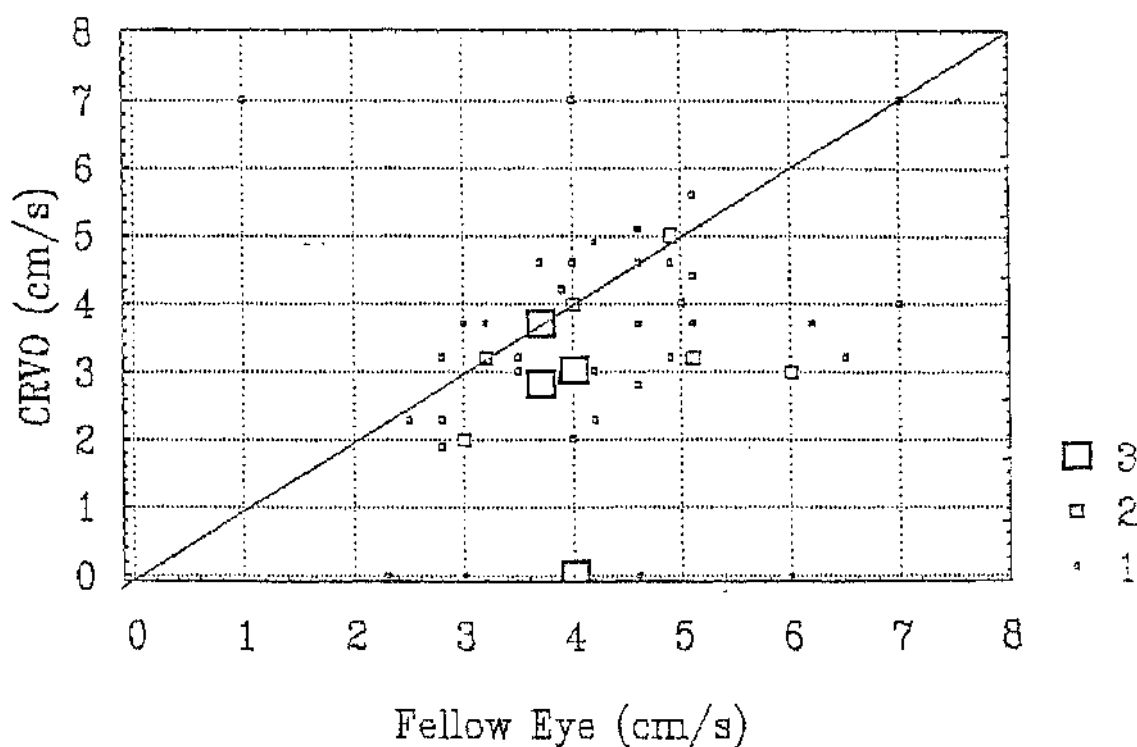


Figure 9.3. A scattergram of Vmin in the central retinal vein of the eyes with CRVO and their unaffected fellow eyes with the points mostly scattered below the line demonstrating that the majority the velocities were lower in the affected eyes than the unaffected eyes. The key shows the number of cases represented by each point.

Retinal Vein Pulsatility

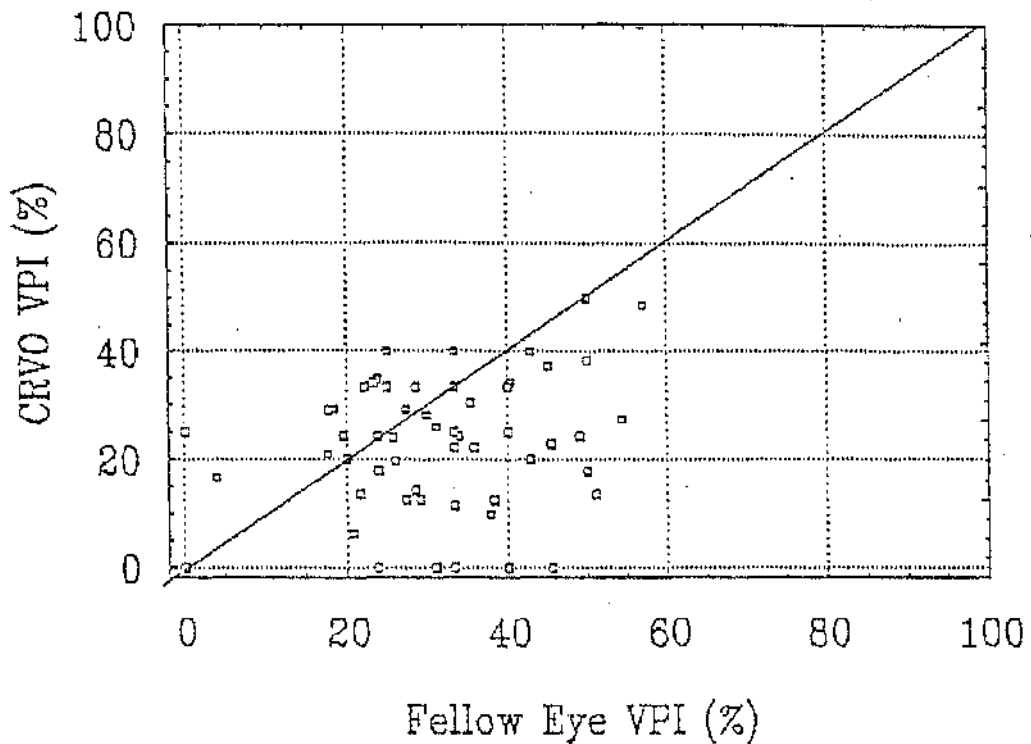


Figure 9.4. A scattergram showing the venous pulsatility indices in the central retinal vein of the eyes with CRVO and their unaffected fellow eyes. The scatter of points below the line illustrates that most of the results were lower the affected eyes than the unaffected eyes. The key shows the number of cases represented by each point.

Age and Sex Matched Comparison

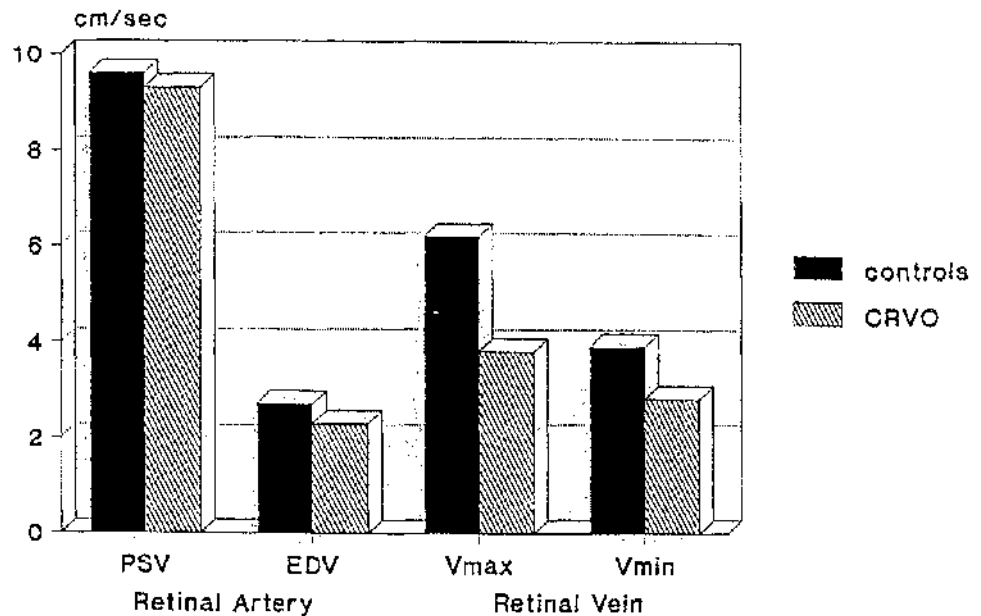


Figure 9.5. The results of the age and sex matched comparison in which significantly lower velocities were found in the central retinal artery and vein of eyes with CRVO than controls (EDV in the retinal artery, $p=0.04$, and Vmax and Vmin in the central retinal vein, $p<0.0001$ and $p=0.002$ respectively).

in eyes with CRVO (table 9.2). In the age and sex matched comparison the venous velocities and the EDV in the central retinal artery were significantly lower (figure 9.5).

Venous pulsatility indices in the central retinal vein were significantly lower in the eyes with CRVO than in the fellow eyes and controls (both $p=0.00001$) despite a significantly higher resistive index in the central retinal artery of the eyes with CRVO ($p=0.02$, figure 9.6). Only the venous pulsatility index in the central retinal vein was significantly lower in the age matched comparison of eyes with CRVO and controls (mean 25.0%, SD 18.4 and 36.5%, SD 9.7 respectively $p<0.001$). These results were also significantly different when the analysis was performed for those patients with nonischaemic CRVO only.

Association with retinal ischaemia.

Forty two eyes were classified as nonischaemic, 26 as ischaemic and 12 as partially ischaemic. Comparison of age, duration, systemic blood pressure, intraocular pressure, keratometry, axial length and refraction showed no significant difference between the eyes with different grades of retinal ischaemia (table 9.3). The values of V_{max} and V_{min} in the central retinal vein reduced as the degree of ischaemia increased and were significantly lower in the ischaemic eyes than in the

Resistive Indices in CRVO

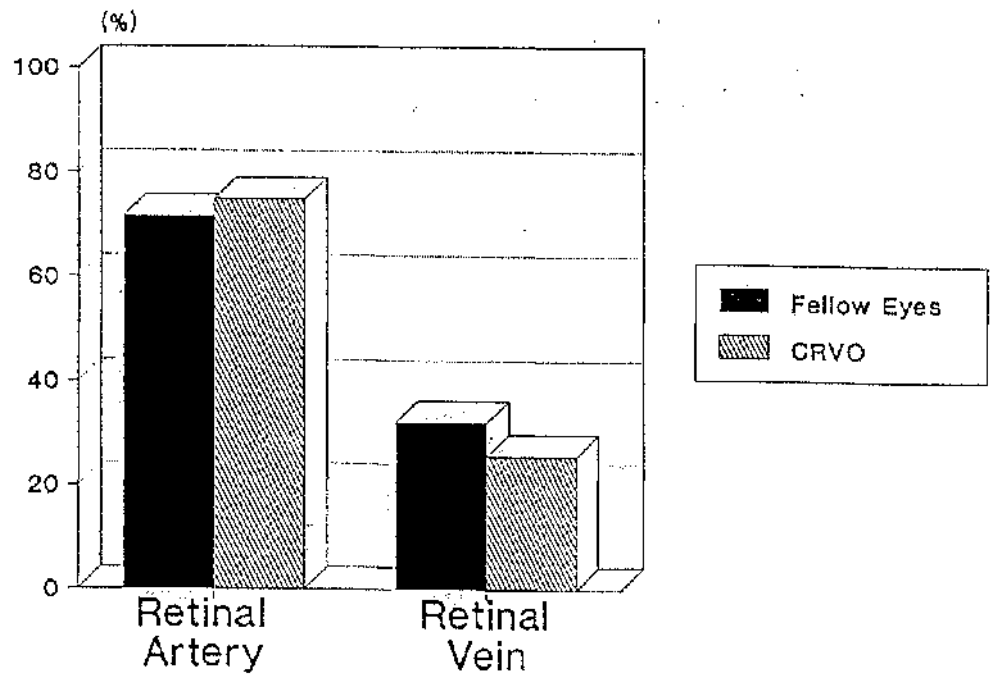


Figure 9.6. A histogram showing the higher mean resistive index in the central retinal artery and the lower mean venous pulsatility index in the central retinal vein in the eyes with CRVO than their contralateral healthy eyes.

Retinal Vein Velocities in CRVO

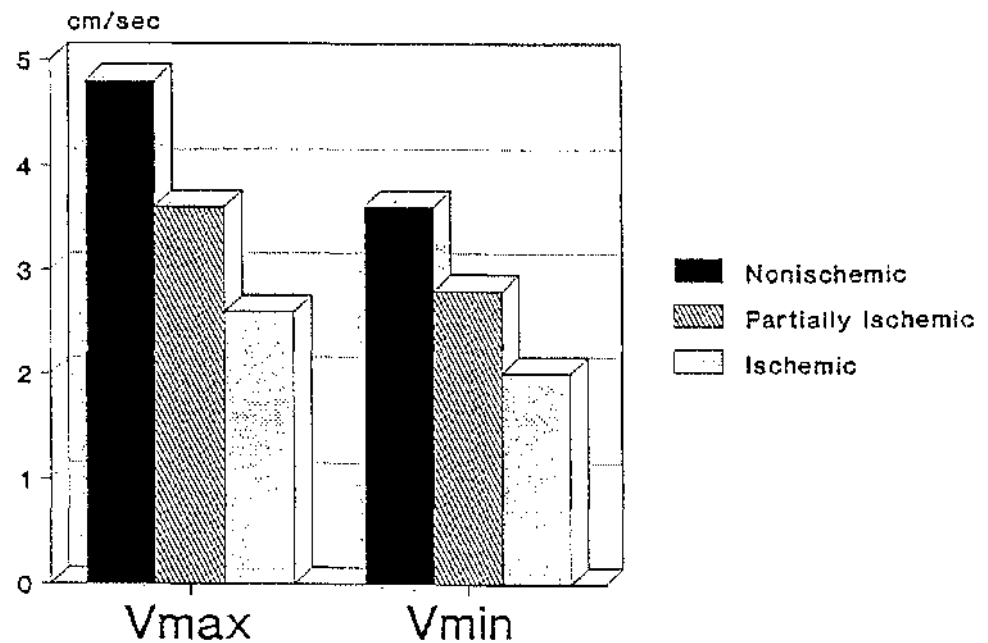


Figure 9.7. A histogram showing the reduction in mean velocities in the central retinal vein as the degree of retinal ischaemia increases.

Table 9.3

	Nonischaemic	Partial Ischaemia (Mean and SD)	Ischaemic
Age (years)	62.1 16.3	69.5 7.0	72.3 9.4
Duration (months)	4.0 5.2	4.3 4.3	4.3 4.4
SBP (mmHg)	145 20.0	157 26.5	155 27.4
DBP (mmHg)	84 9.6	81 16.5	90 12.4
IOP (mmHg)	16.1 4.2	17.5 5.1	15.7 4.6
AXIAL LTH (mm)	22.9 1.1	22.3 1.4	22.2 1.2
KERATOMETRY (Dioptres)	43.6 1.2	43.2 1.3	44.1 1.8
REFRACTION (Dioptres)	0.6 2.6	1.1 4.0	0.5 3.1

Table 9.3. General data are presented showing similarities between the patients with different classifications of ischaemia.

nonischaemic eyes ($p=0.01$ and $p=0.003$ respectively, figure 9.7). This was also found after analysis of covariance for age which was used to compensate for an insignificant trend for increased age in the ischaemic CRVOs. Flow in the central retinal vein was undetectable in 11 eyes, all of which had suffered ischaemic or partially ischaemic occlusions.

Prediction of the Development of Iris Neovascularisation.

The results from patients examined within three months of onset were investigated to determine the capability of the tests to predict the development of iris neovascularisation. The results from five patients were excluded, three patients who presented with new vessels of the iris at the first visit, two who were subsequently treated with prophylactic panretinal photocoagulation and one who developed retinal new vessels. The

V_{min} in the central retinal vein was significantly lower in the 8 patients who went on to develop iris neovascularisation than those who did not (mean 1.9 cm/sec, SD 1.8, and mean 3.5 cm/sec, SD 0.7, respectively, $p=0.02$). The one patient who developed retinal neovascularisation also had a low V_{min} of 2.8 cm/sec. The presence of a V_{min} of less than 3.0 cm/sec in the central retinal vein in these patients was found to provide a high predictive value for the development of

iris neovascularisation with a sensitivity of 75% and a specificity of 86% (figure 9.8). This was superior to conventional tests in this group for which sensitivities and specificities are shown in the table 9.4. Furthermore four patients could not be assessed by RAPD measurement (two because of bilateral CRVO and two because of ocular disease in the fellow eye) and six patients by fundus fluorescein angiography (because of poor agreement between observers or poor visualisation of retinal detail) thereby reducing the applicability of these tests.

Prediction of Visual Acuity Recovery.

The results from patients examined within three months of onset of the disease (37 patients) were also used to determine the use of the various tests for the prediction of visual recovery. The visual acuity at presentation had the highest predictive value for the final visual acuity with a sensitivity of 85% and specificity of 75% for obtaining 6/24 visual acuity or better if the presenting visual acuity was 6/24 or better. This was primarily because 51% of the patients showed no change in their visual acuity over the year. In seven of the patients the visual acuities reduced over the year, five of these patients had values for Vmin in the central retinal vein which were less than 3.0 cm/sec (figure 9.9). In addition, seven of the

ROC Curve for the Prediction of Rubeosis Vmin

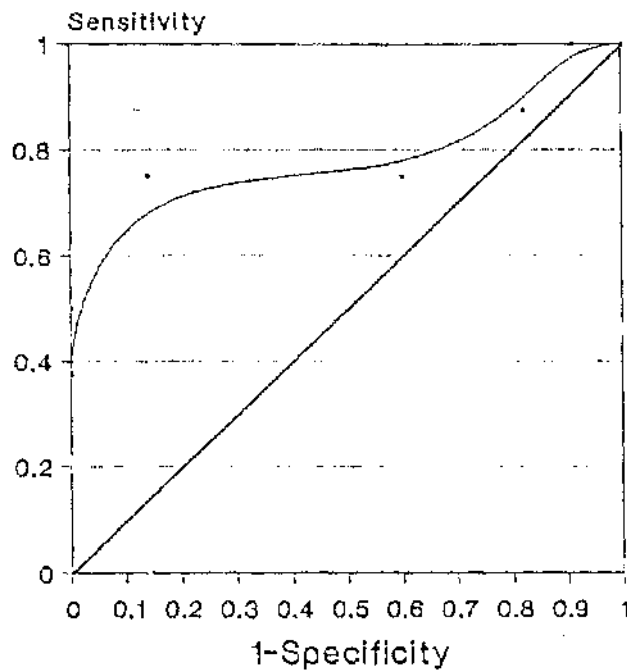


Figure 9.8. A receiver operator characteristic curve for the prediction of iris neovascularisation from values of V_{min} in the central retinal vein.

Table 9.4

	Unassessable Patients	Sensitivity	Specificity (%)
Color Doppler Imaging	0	75	86
Electroretinography	0	67	92
RAPD Measurement	4	71	79
Fluorescein Angiography	6	60	67
Visual Acuity	0	50	45
Ophthalmoscopy	0		
Cotton Wool Spots (Presence v Absence)		25	45
Retinal Haemorrhages (Mild v Moderate or Severe)		33	27

Table 9.4. Prediction of the Development of Rubeosis in patients with less than three months from the onset of the occlusion. The sensitivity and specificity values are shown and indicate that the presence of low velocity (V_{min}) in the central retinal vein measured by Color Doppler Imaging provides the best prediction of iris neovascularisation. Some patients were unassessable by RAPD measurement or fluorescein angiography and were excluded from the calculations.

Prediction of Deterioration in VA

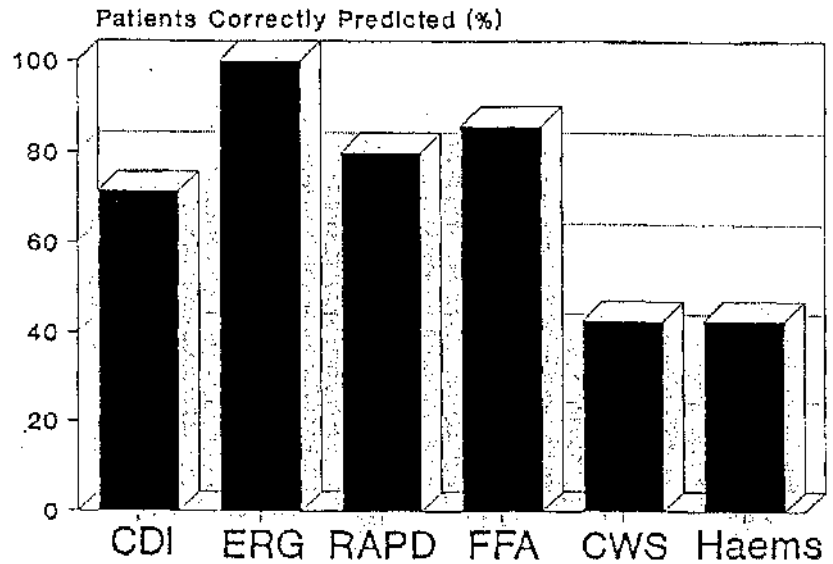


Figure 9.9. A histogram showing the percentage of the patients who suffered a loss of visual acuity and in whom an "ABNORMAL" result was detected by the various tests.

Prediction of Improvement in VA

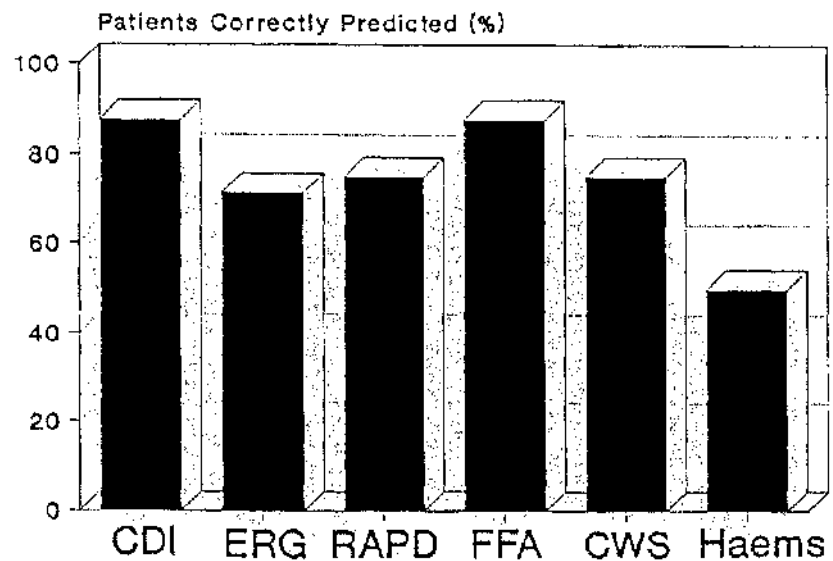


Figure 9.10. A histogram showing the percentage of the patients whose visual acuity improved and in whom a "NORMAL" result was detected by the various tests.

eight patients with improvement in their acuity had V_{min} above this value (figure 9.10). These results were reflected in the calculation of venous pulsatility index in the vein which was higher in those patients who lost visual acuity than those who improved ($p=0.04$).

The Fellow Unaffected Eye.

Analysis of covariance for age determined that the venous pulsatility index in the vein was significantly lower in the central retinal vein of the fellow eyes compared to the controls ($p=0.007$, figure 9.11) but this result was not significant in the age matched case controlled comparison. In an examination of the control population there was a positive correlation between the resistive index in the central retinal artery and that in the vein ($r=0.34$ $p=0.0008$). The correlation between the resistive indices was less in the fellow eyes of the CRVO patients ($r=0.27$, $p=0.03$) than in the controls. In the case controlled study the resistive index in the ophthalmic artery was significantly higher in the fellow eyes compared with the controls (76.9 cm/sec, SD 7.0, and 73.5 cm/sec, SD 8.5 respectively $p=0.05$). In addition an increase in this measure with age ($r=0.27$, $p<0.05$) was found in the patients but not the controls.

9.5 Discussion

Venous Pulsatility in The Control and Fellow Eyes

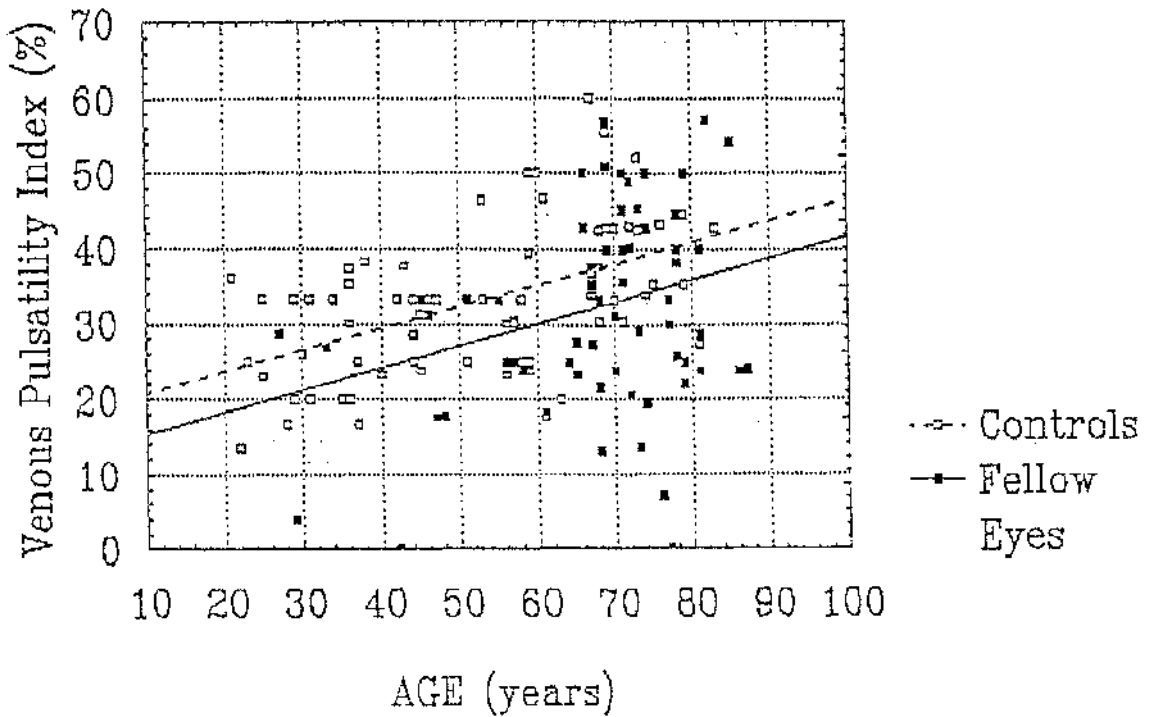


Figure 9.11. A scattergram showing the difference in the venous pulsatility index in central retinal vein in the unaffected fellow eyes of patients with CRVO and the control population. The linear regression lines show an increase in the index with age and illustrate that the results from the patients are lower.

In this study the blood velocities in patients with central retinal vein occlusion were examined by color Doppler imaging to determine the influence of the condition upon blood flow in the eye and to determine the applicability of CDI as a clinical tool for the investigation of CRVO. The results were analysed for the prediction of visual recovery and development of iris neovascularisation. In the latter particularly the system could be applied effectively with advantages over conventional tests. The results of the patients examined less than three months from onset of the occlusion were used because the blood velocities measured by colour Doppler imaging can reasonably be expected to change as the recanalisation of the vessels occurs. For the prediction of the development of iris neovascularisation the measurement of blood velocity in the central retinal vein in those examined within three months of onset of the occlusion provided higher sensitivities and specificities than the conventional tests (75% and 86% respectively for V_{min} less than 3.0 cm/sec). In addition one patient who developed retinal neovascularisation also had a low V_{min} value (2.8 cm/sec).

Unlike fundus fluorescein angiography the investigation is noninvasive and is unaffected by retinal haemorrhaging or opacification of the media which often prevent

adequate assessment of angiograms (8% of cases in this study and up to 33% in another study) ¹⁰⁴. Capillary closure may not be detectable on fluorescein angiography until three months after the onset of the occlusion which explains the poor predictability of this test in the patients with recent presentation (sensitivity 60% and specificity 67%). The usefulness of the fluorescein angiography is further reduced because poor agreement frequently exists between assessments of ischaemia by the same observer ²⁹⁵. The other tests also have drawbacks, for example, relative afferent pupillary defect measurement can only be applied to cases of unilateral CRVO when the fellow eye is healthy, preventing its use in 15.3% of the cases in this study. Electroretinography produces a variety of predictive values, depending on the test strategy used but requires a prolonged examination procedure 22,126,201,241. CDI can therefore be used to determine the outcome for patients with CRVO and is superior to conventional methods of investigation in the prediction of iris neovascularisation for patients examined within three months of onset of the disease.

The visual acuity at presentation in these patients provided the best indicator of the visual acuity at one year because the majority (51%) showed no change. However, a large proportion (87.5%) of the patients who showed an increase in their visual acuity had a Vmin in the central retinal vein of 3.0 cm/sec or greater and

similarly most of those (71%) in whom the visual acuity decreased had V_{min} less than 3.0 cm/sec.

The reduction in the blood velocities in the retinal circulation of eyes suffering from CRVO was greatest in the vein and was most marked in those patients with ischemia of the retina. Although there was a significant reduction in the velocities in the central retinal artery this was smaller than in the vein and did not vary with the degree of retinal ischemia. As yet the resolution of the color Doppler equipment is not sufficient to determine the diameter of vessels as small as these and therefore extrapolation of the Doppler results to the blood flow in the vessel must be performed with care. Any change of the cross sectional area of a vessel will profoundly affect the velocity of the blood if constant laminar blood flow is assumed. The central retinal artery and vein in the optic nerve are however surrounded by a thick collagenous adventitia reducing the chance of temporary collapse or dilation of these vessels. Calculation of the cross-sectional area of the vein from a diametric measurement of the vessel in any case would be frequently inaccurate because the vein's cross-sectional profile in the optic nerve varies from crescentic to oval ²⁶⁹. It is possible that the velocities in the central retinal vein reflect the changes in the retinal circulation more accurately than

those from the muscular artery which may have dilated in response to relative ischemia of the retina or constricted in an attempt to maintain a constant pressure in the capillaries.

Doppler examination of the central retinal artery and vein within the optic nerve provides some technical advantages because their straight course aids the reliability of Doppler measurements and allows angle correction to be applied (figure 9.12). In CRVO the pathological changes in the vessels occur in the region of the lamina cribrosa ^{79,134}. The blood velocities were measured posterior to this site, therefore providing a measure of the changes in blood flow resulting from the constriction. It is tempting to suggest that the decrease in venous pulsatility index in the vein signifies an increase in the resistance to flow upstream of the measurement site, ie., from blockage or constriction of the vein at the lamina cribrosa. In the vein however this explanation is of doubtful validity because the intraocular retinal venous velocity described by laser Doppler velocimetry is nonpulsatile ²³¹ and in an anomalous hemiretinal vein with an extraneural course non pulsatile flow is present (chapter 6). The pulsations in the venous flow in the vein in its intraneural course result probably because the artery increases the velocity in the vein because of its close proximity to the vein, ie., the artery expands during systole reducing the cross-

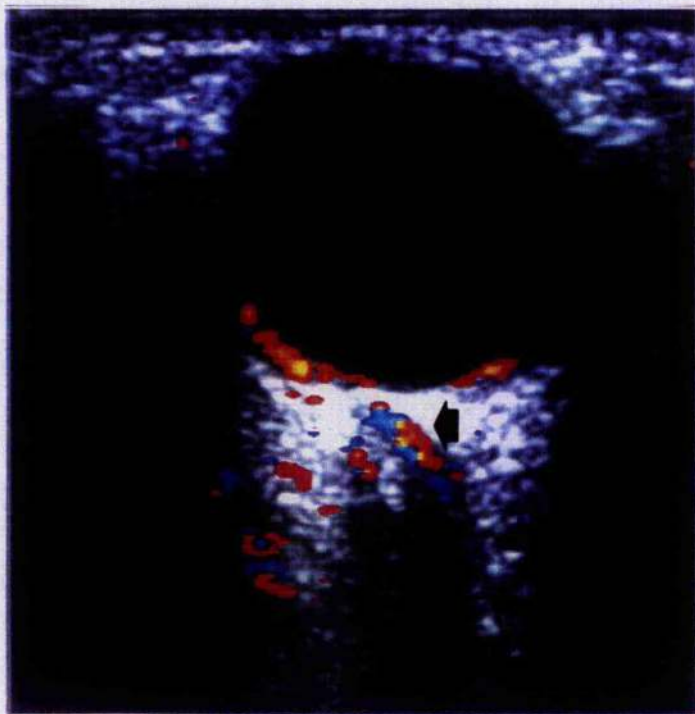


Figure 9.12. Normal. The central retinal artery and vein in the optic nerve are indicated on the Bscan image by red and blue coloured pixels respectively (arrow).

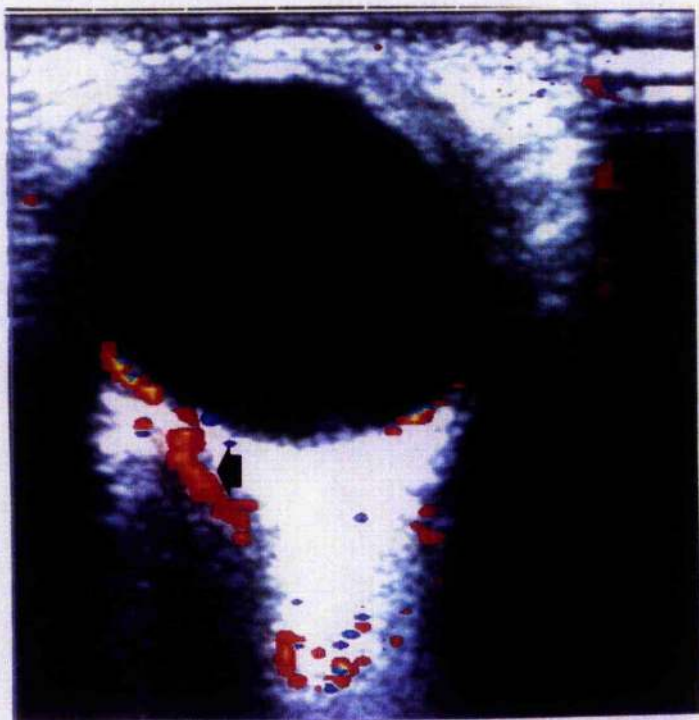


Figure 9.13. Ischaemic CRVO. Only flow in the central retinal artery (red) can be detected no venous flow (blue) is seen (arrow).

sectional area of the vein thereby increasing the blood velocity. The reduction in the values for venous pulsatility index in the veins of the affected and contralateral unaffected eyes in CRVO shows that this effect has been lessened in these patients.

The observation of undetectable or reduced blood velocity in the central retinal vein of eyes with CRVO despite maintained blood velocity within the central retinal artery may be explained by blood bypassing the occluded central retinal vein via collateral venous channels. Indeed 20% of the patients demonstrated dilated collateral channels at the optic nerve head on fundoscopy. These channels are multiple, small in calibre and in most circumstances beyond the resolution of CDI. Alternatively, low flow may still have been present in the central retinal vein but was beyond the resolution of the machinery ^{270,302}. Blood velocities in the central retinal vein were further reduced or undetectable in those eyes with ischaemia of the retina (figure 9.13), indicating that the "occlusion" in these cases was more severe.

A lower venous pulsatility index was detected in the central retinal vein of the fellow unaffected eyes than in the controls. This may predispose the retinal circulations of these patients to stasis of blood flow explaining the risk of bilateral disease in 6- 16% ^{50,222,239}. Since the changes in velocity in the vein

are likely to be induced by the pulsation of the artery this may be a sign that the venous velocity in these patients is less able to change. Possibly this is caused by increased blood viscosity reducing the rapidity with which the blood can change its velocity 227,278. Alternatively, stiffening of the arterial or the venous wall from sclerotic degenerative changes 4,50 could be reducing the expansion of the artery during systole and therefore the degree of alteration in velocity in the vein. Evidence of peripheral arterial disease on CDI was provided by the increased resistive index in the ophthalmic artery of the fellow eyes.

In summary, CDI allowed simultaneous examination of the central retinal vein and artery in patients with CRVO. The pattern of blood velocity changes indicates a predominant disruption to the flow in the central retinal vein and to a lesser degree in the central retinal artery. The blood velocities in the vein can be used to help determine the likelihood of visual recovery. Finally the presence of a low velocity in the vein can be used to predict the development of iris neovascularisation and is superior in this aim than conventional tests. The results indicate that noninvasive color Doppler imaging could replace the invasive procedure of fundus fluorescein angiography as the routine method of assessing patients with CRVO with less than three months from onset of the occlusion.

10 Chapter 10

A COMPARISON OF COLOUR DOPPLER IMAGING OF ORBITAL VESSELS AND OTHER METHODS OF BLOOD FLOW ASSESSMENT.

10.1 Summary.

A comparison of the haemodynamic measurements obtained by colour Doppler imaging and other methods of ocular blood flow measurements was made. The blood velocities from colour Doppler imaging of patients with central retinal vein occlusion were compared with the results of video fluorescein angiography, continuous tonography and ophthalmodynamometry. Patients with low or undetectable blood velocities in the central retinal vein had longer retinal dye transit times on video angiography. Tonographic readings showed a positive correlation with the velocities in the ophthalmic artery but ophthalmodynamometric results showed a negative correlation. The velocities from colour Doppler imaging of the central retinal vein may provide a more accurate indicator of the blood flow in the retina than the artery perhaps because the muscular artery actively undergoes changes in diameter in response to disease processes. The ophthalmic artery blood velocities provide an alternative to other methods for the assessment of blood flow in the ophthalmic artery.

10.2 Introduction.

A comparison of colour Doppler imaging with other methods of blood flow assessment in the eye and orbit is required in order to enhance the interpretation of the velocity measurements. In this study, the relationships between fluorescein video angiography, continuous tonometry and ophthalmodynamometry, and colour Doppler imaging of the ophthalmic artery and the central retinal artery and vein was investigated in patients with central retinal vein occlusion. The results obtained by these different methods are compared and contrasted.

10.3 Patients and Methods

A cohort of 54 patients who had suffered central retinal vein occlusion, at most 6 months previously, underwent both colour Doppler imaging and fluorescein videoangiography of the affected eyes. The mean age of the patients was 68.8 years (SD 11.8 years) with 25 males and 29 females. The mean systemic blood pressure was 151.3 mmHg (20.6 mmHg) and diastolic blood pressure was 80.3 mmHg (SD 11.5 mmHg). Sixteen of these patients also consented to continuous tonometry and ophthalmodynamometry and the results were compared to velocity results from colour Doppler imaging. Ethical committee approval had been granted and informed

consent was obtained before each examination. The study conformed to the principles established in the Declaration of Helsinki.

Colour Doppler Imaging.

The examination method for colour Doppler imaging has been fully described previously in chapter 3.

Fluorescein Videoangiography.

A Rodenstock Scanning Laser Ophthalmoscope (SLO) was used to obtain fluorescein video-angiograms on 54 patients with central retinal vein occlusion. The pupils were dilated with topical Tropicamide 0.5%. Recordings of the images were stored on Umatic magnetic video tape. In the first instance Helium neon laser was used to focus the laser upon the retina. The laser was then changed to Argon green and 3 mls of 20% sodium fluorescein was injected at rate of 1 ml/sec through an intravenous 23 gauge butterfly inserted into an antecubital vein. At the start of the injection the timer of the SLO was commenced and the video recording started. Images of the optic disc area using a 40 degree field of view were taken whilst the dye entered the retinal circulation and until the dye had faded from the retinal veins. Six views of the peripheral retina were then recorded. Two measures of the flow of blood plasma in the retinal circulation were obtained

by observing the appearance of fluorescein dye in the retinal vessels:

The Retinal Transit Time (RTT) - The time between the first appearance of dye in a hemiretinal artery at the optic disc margin and the first appearance of dye in the adjacent hemiretinal vein.

The Time to Maximal Venous Filling (TMVF) - The time between the first appearance of dye in the hemiretinal artery and the time when the maximal fluorescein concentration is seen in the adjacent hemiretinal vein. These two measures were estimated by an observer who was masked to the clinical and investigative results of the patients.

Tonography

Intraocular pressure variation during the systemic pulse was recorded in 32 eyes (16 affected by central retinal vein occlusion and 16 contralateral unaffected eyes) using a Digilab 30R pneumotonometer. The amplitude of the intraocular pressure rise is dependent on the change in blood volume in the choroid and has been used as a measure of the pulsatile component of the ophthalmic artery blood flow 152,252.

Before each examination the tonometer was recalibrated using calibration apparatus which applies a known pressure onto a diaphragm. The tonometer was applied to the diaphragm and the marker needle of the recording paper adjusted accordingly. Benoxinate 0.4% was in-

stilled into the eyes of each patient who was positioned supine. The tonometer was applied to the cornea and continuous IOP recordings obtained over three respiratory cycles. Recordings were obtained from both eyes of each patient.

Ophthalmodynamometry

The diastolic blood pressure was estimated in the ophthalmic artery using a Yablonski Fundus Lens Ophthalmodynamometer (Varian, Clinitex division) in 19 eyes of 12 patients (ten with central retinal vein occlusion and nine contralateral unaffected eyes, one was excluded because of the presence of a longstanding retinal detachment). In four patients the examination was abandoned because of poor visualisation of the vessels or tolerance of the test. The pupils were dilated with topical Tropicamide 0.5% and the corneas anaesthetised with Benoxinate 0.4%. The patient was placed in the examination position on a slit lamp and the maximum force indicator on the ophthalmodynamometer was set to zero. Whilst viewing the hemiretinal arteries at the disc through the contact lens an increasing force was gradually applied to the lens by means of the sprung lever of the instrument until the arteries began to pulsate. The force was then released, the maximum force was recorded in grams by the maximum reading indicator needle on the dial. The

procedure was repeated on three occasions for each eye and the results averaged. The results obtained by ophthalmodynamometry are considered to provide the diastolic blood pressure momentarily of the central retinal artery but after a few seconds of sustained pressure the readings are thought to be of ophthalmic artery blood pressure ^{71,185}. The results were therefore converted into the ophthalmic artery perfusion pressure by converting the values into diastolic blood pressure (3.1g/mmHg diastolic blood pressure) and subtracting the intraocular pressure:

$$\text{Diastolic Perfusion Pressure} = (\text{Force}/3.1) - \text{IOP}$$

Statistical Methods

Nonparametric statistical tests were employed using Mann Whitney U test, Wilcoxon Matched pairs test and Spearman rank correlation where appropriate.

10.4 Results

Colour Doppler Imaging

The results from the patients used in the comparison with videoangiography are provided in table 10.1, and with ophthalmodynamometry and tonometry in table 10.2. Even in the small sample size used in the comparison of colour Doppler imaging with tonography and ophthalmodynamometry there were significant differences between the velocities from the retinal vessels in the eyes

Table 10.1

	PSV (cm/sec)	EDV	Resistive Index (%)
Eyes with CRVO			
Ophthalmic Artery			
	39.0 (11.4)	9.2 (3.9)	76.6 (6.7)
Retinal Artery			
	9.2 (3.2)	2.3 (1.5)	74.5 (12.1)
Retinal Vein			
	3.9 (2.3)	2.9 (1.7)	24.4 (13.3)

Table 10.1 The velocity results from colour Doppler imaging of the thirty eight patients used in the comparison with the videoangiography.

Table 10.2

	PSV (cm/sec)	EDV	Resistive Index (%)
Eyes with CRVO			
Ophthalmic Artery			
	37.3 (11.6)	9.5 (4.6)	75.0 (7.8)
Retinal Artery			
	9.7 (3.0)	2.2 (1.0) #	75.6 (11.9)
Retinal Vein			
	3.7 (2.0) *	2.5 (1.6) *	29.0 (24.1)

Fellow Unaffected Eye

Ophthalmic Artery			
	38.2 (12.1)	9.6 (4.9)	75.8 (5.9)
Retinal Artery			
	10.9 (3.0)	3.1 (0.9) #	70.8 (8.3)
Retinal Vein			
	6.4 (2.7) *	4.1 (1.2) *	32.0 (14.2)

Table 10.2 The colour Doppler results are provided for the patients who were used in the comparison with ophthalmodynamometry and tonography. Despite the small sample size (n=16) there were significant differences between the results from the affected eyes and the fellow unaffected eyes for the venous velocities (* p=0.001) and for the EDV in the central retinal artery (# p=0.005).

affected by the venous occlusion and their fellow unaffected eyes.

Fluorescein Angiography

Fifty four patients were examined but in 16 the examination of dye transit times was inadequate because of poor visualisation due to medial opacities, blinking or eye movements. Thirty eight eyes affected by central retinal vein occlusion of 38 patients had fluorescein videoangiograms from which the two subjective measures of the flow of dye through the retinal circulation, time to maximum venous filling and retinal transit time were elicited.

The mean retinal transit time was 5.9 seconds (SD 2.4) and the mean time to maximal venous filling was 15.7 seconds (SD 4.8). No correlation was found between the Doppler results from the ophthalmic artery and central retinal artery and the results from the videoangiograms (using Spearman rank correlation). The Doppler results from the central retinal vein provided undetectable flow velocities from eight patients in whom blood flow may have been present. To allow comparison, the fluorescein results from those patients with V_{min} velocities greater than 3.0 cm/sec were compared to the rest of the group (similarly 4.0 cm/sec was used as the cutoff for V_{max}). The mean time to maximal venous filling for the 16 patients with a V_{min} of more than

3.0 cm/sec was significantly shorter than the mean result for the rest of the group (mean 13.4 secs, SD 4.4 and mean 16.6 secs, SD 3.8, respectively $p=0.02$). Also the mean macular transit time for the 19 patients with a Vmax of greater than 4.0 cm/sec was significantly shorter than the mean for the rest of the group (mean 5.0 sec, SD 2.3 and 6.8 sec, SD 1.7, respectively $p=0.02$).

Tonography

Thirty two eyes from sixteen patients were examined by tonography. The mean intraocular pressure amplitudes in the eyes with central retinal vein occlusion and their fellow eyes were statistically similar (1.02 mmHg, SD 0.8 and 0.83 mmHg, SD 0.6 respectively). Figures 10.1 and 10.2 illustrate that the amplitude of spontaneous intraocular pressure variation was found to positively correlate with the Doppler measurements of velocity in the ophthalmic artery (peak systolic velocity $r=0.63$, $p=0.0004$, figure 10.1, and end diastolic velocity $r=0.54$, $p=0.004$, figure 10.2). None of the other Doppler results showed any correlation with tonometry.

Ophthalmodynamometry

Nineteen eyes of 12 patients were successfully examined by ophthalmodynamometry which provided a measure of the diastolic perfusion pressure in the central retinal

Pulsatile Blood Flow

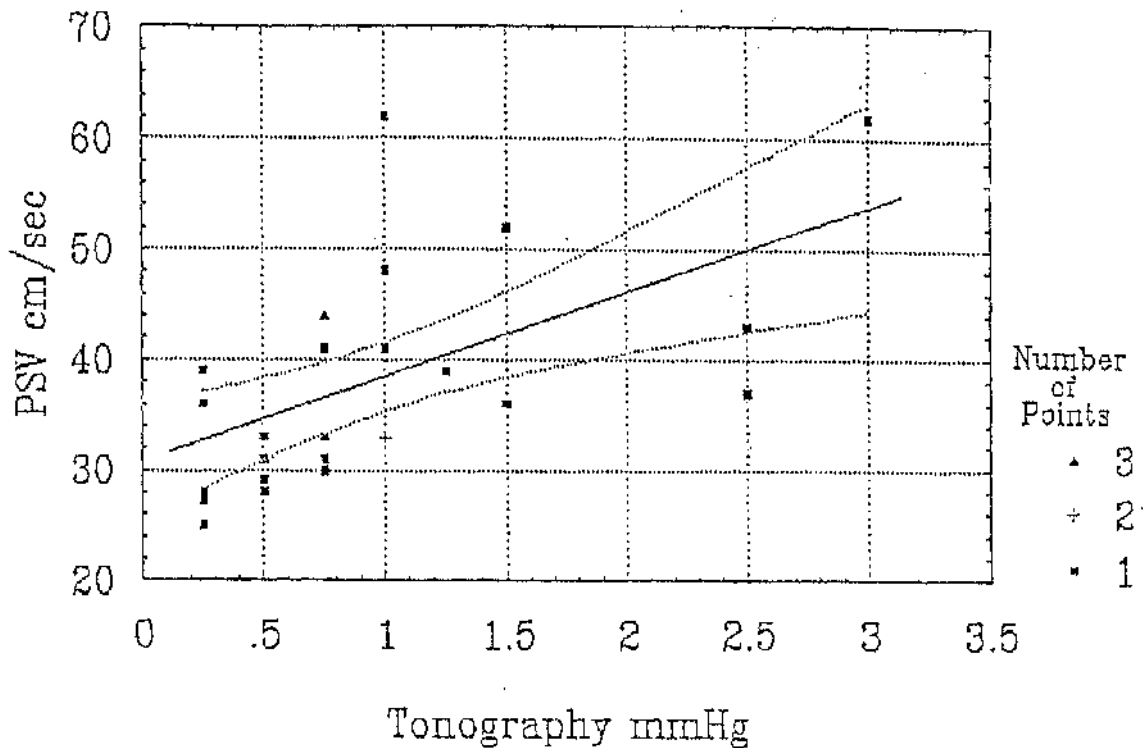


Figure 10.1. The peak systolic velocities in the ophthalmic artery positively correlated with the intraocular pressure variations in the eye which are thought to result from the pulsatile component of the choroidal blood flow ($r=0.63$). A linear regression line and 95% confidence levels are shown.

Pulsatile Blood Flow

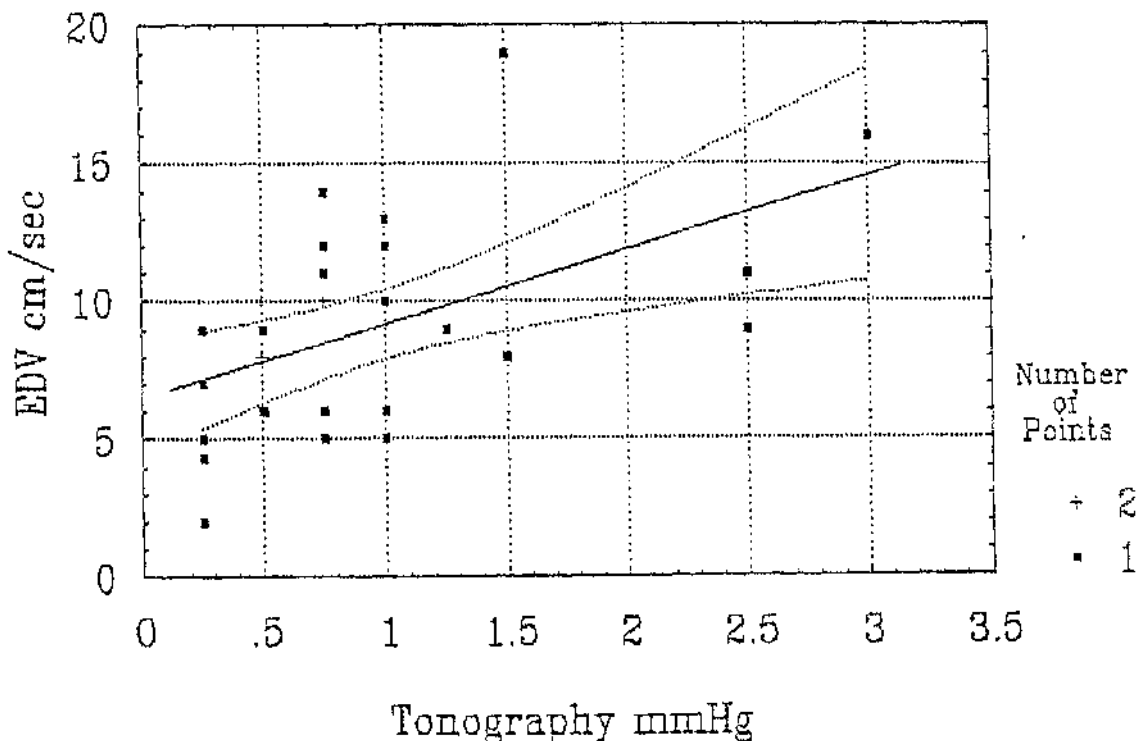


Figure 10.2. The end diastolic velocities in the ophthalmic artery correlated with the intraocular pressure fluctuations ($r=0.54$). A linear regression line and 95% confidence levels are shown.

artery and indirectly in the ophthalmic artery. Attempted examination of the other eyes failed because of poor tolerance of the test in two patients, cataract in four eyes and poor pupillary dilation in two eyes. The mean diastolic perfusion pressures in the eyes with central retinal vein occlusion and their fellow eyes were statistically similar (35.9 mmHg, SD 12.2 and 38.5 mmHg, SD 8.2 respectively). The results from one patient were found to have a much reduced diastolic perfusion pressure (10 mmHg) with relatively high ophthalmic artery velocities (PSV 62 cm/sec and PEDV 16 cm/sec) perhaps signifying a localised stenosis of the artery. This patient was removed from the Spearman rank correlation as an outlying point. Correlations were detected between the diastolic perfusion pressure and the EDV and resistive index in the ophthalmic artery (end diastolic velocity $r=-0.54$, $p=0.02$ and resistive index $r=0.47$, $p=0.05$, figure 10.3).

10.5 Discussion

There is no direct method for the measurement of blood flow in the orbit and so many indirect methods have often been devised. In this study three established techniques for the estimation of different parameters of blood flow in this region were compared to the blood velocity measurements obtained by colour Doppler imag-

Diastolic Perfusion Pressure

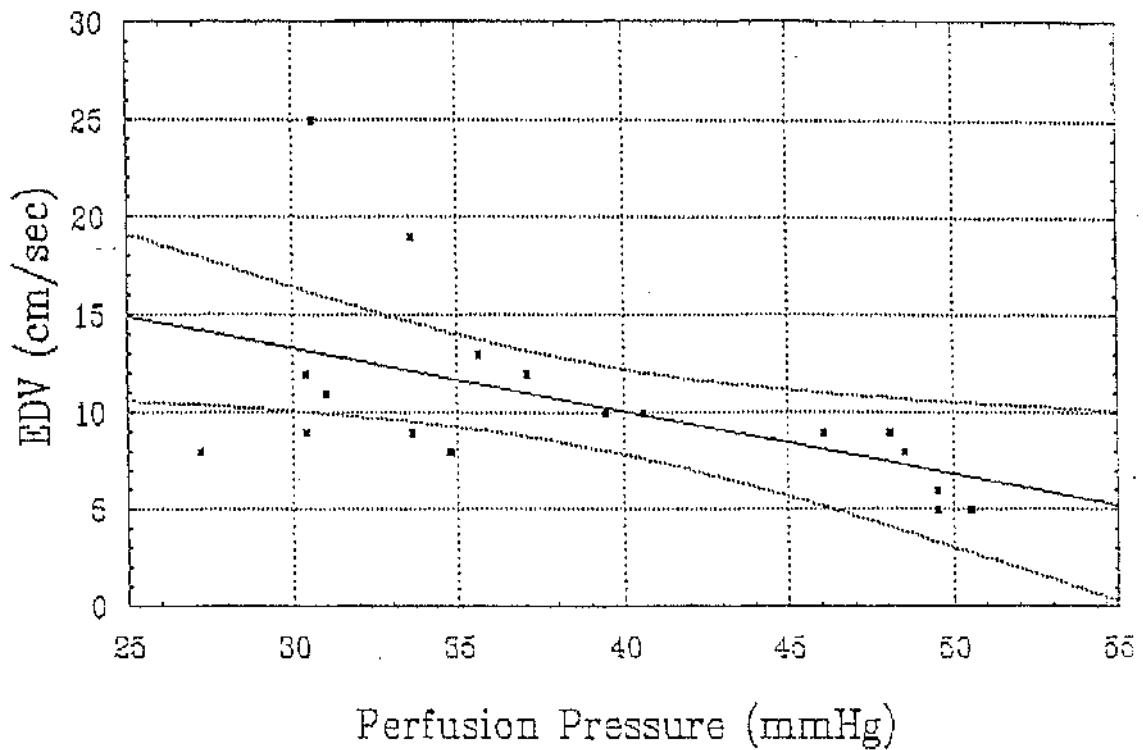


Figure 10.3. The diastolic velocities in the ophthalmic artery (EDV) are illustrated showing a negative correlation with the perfusion pressure during diastole in the vessel measured by a Yablonski ophthalmodynamometer ($r=-0.52$). A linear regression line and 95% confidence levels are shown.

ing. Correlations were found between the Doppler measurements and the other measures of the haemodynamics in the ophthalmic and retinal circulations obtained by ophthalmodynamometry, continuous tonometry and fluorescein angiography.

The mainstay of clinical vascular investigation of the human retinal circulation is fluorescein angiography. In this study, the time required for the dye to pass through the circulation was recorded as a measure of how rapidly the dye passes from the arterioles to the venules of the retina and is presumably related to the rapidity of blood flow in this circulation. Comparison of the Doppler results and the videoangiographic results by linear correlation was not possible when examining the blood velocities in the vein because of the significant number of patients with undetectable blood velocities. However there were significantly longer dye transit times for those patients with low V_{max} or V_{min} results than those with higher results. In this simplified comparison with its obvious inadequacies there appears to be some relationship between the rapidity of the dye transit and the velocities in the vein. In contrast the velocities in the central retinal artery showed no correlation with the fluorescein dye transit times. This finding could be due the occurrence of a secondary change in the diameter of the central retinal artery as was suggested in chapter 9, which altered the measured velocity of

the blood thereby explaining the poor correlation with angiography. The thin walled amuscular vein cannot actively change its diameter. Therefore the velocity of the blood in this vessel may provide a better indicator of changes in the perfusion of the retina.

A variety of methods have been devised for the estimation of the pulsatile component of total ocular blood flow from the variations that occur in intraocular pressure with the systemic pulse using tonography^{152,252}. A number of assumptions have been made^{113,252} but the volume changes are thought to result primarily from the expansion of the choroidal vasculature during the ingress of blood with the systemic pulse^{112,252}. The choroidal circulation takes the majority of the ocular supply from the ophthalmic artery, therefore the IOP amplitudes have been used to measure the pulsatile component of the ophthalmic artery blood flow to the eye. In this study the amplitude of the intraocular pressure rises measured by tonography demonstrated a positive correlation with the velocities measured by Doppler in the ophthalmic artery. Since the retinal circulation takes only a small proportion of the ocular blood flow from the ophthalmic artery, approximately 2-5%¹¹¹, it is not surprising that this measure of ophthalmic artery blood flow showed no correlation with the retinal blood velocities.

Finally ophthalmodynamometry was used to measure the diastolic ophthalmic arterial blood pressure using a contact lens technique. The results are contrary to the expectation that as the perfusion pressure increases the blood flow and therefore the blood velocity increases. In this study the velocity in the ophthalmic artery negatively correlated with the perfusion pressure during diastole. This may be due to the inherent inaccuracies of both techniques or is a warning that we cannot assume that increased blood velocity means increased blood flow. For example, undetected changes in the diameter of the blood vessels may have result in increased blood velocities despite a reduction in perfusion. The positive correlation between the resistive index in the ophthalmic artery and the perfusion pressure suggests increased peripheral resistance to flow which may have caused systemic hypertension in these patients. This may have increased the perfusion pressure despite a reduction in the blood flow to the tissue. Whatever the explanation the finding illustrates the complexity of the relationship of haemodynamic parameters in the human. In summary, the velocities in the ophthalmic artery correlated positively with the intraocular pressure variations induced in the eye by the pulsatile blood flow in the ophthalmic artery. In contrast the perfusion pressure was negatively correlated with the ophthalmic artery velocities. The blood velocities

from the central retinal vein varied with the passage of fluorescein dye through the retina but those from the artery did not.

11 Chapter 11

BLOOD VISCOSITY AND COAGULATION IN CENTRAL RETINAL VEIN OCCLUSION: A POPULATION CONTROLLED STUDY.

11.1 Summary

The role of blood viscosity and coagulation has been investigated in the past in studies consisting of patients with central retinal vein occlusion (CRVO) and branch vein occlusion and with conflicting results. This may have been in part due the presence of differing aetiological factors in these two types of vein occlusion. In this study viscosity and coagulation were re-examined in 69 patients with CRVO only and compared to the results from an age-matched, population based control group. Viscosity variables were higher in CRVO than controls (in particular relative blood viscosity) suggesting (in the presence of similar red cell aggregation) that reduced red cell deformability was associated with the occurrence of CRVO. Patients who developed the complication of iris neovascularisation had relatively low antithrombin III, factor VII and tissue plasminogen activator indicating both a tendency to thrombus formation and a reduction in fibrinolytic activity. In most patients with CRVO there may be an increased risk of CRVO because of raised blood viscosity and in some patients particularly those who developed complications abnormalities of haemostasis may be present. A proposal is made that

stasis of flow occurs in these patients with thrombus formation only in at risk individuals who go on to develop iris neovascularisation.

11.2 Introduction

Blood viscosity is an important determinant of blood flow and may be a contributory factor in the production of a number of vascular diseases of the eye. A clinical association between central retinal vein occlusion (CRVO) and raised blood viscosity exists because the systemic hyperviscosity syndromes often present with retinal features which are similar to CRVO such as venous engorgement, retinal haemorrhages, disc hyperaemia and macular oedema

8,38,62,139,193,236,243,261. Indeed in some cases the retinal appearance cannot be distinguished from CRVO 7,272. The retinopathy only occurs when the blood viscosity is high ²⁴⁰ and resolves when therapy reduces the viscosity ^{81,174}. Another link with CRVO and viscosity has been provided by the association between the systemic conditions commonly found in central retinal vein occlusion, e.g., systemic hypertension, and abnormal rheology ¹³⁹.

There have been a number of studies examining the role of blood viscosity and haemostasis in patients with retinal vein occlusion, most of which have included

mixed groups of patients with branch retinal vein occlusion and CRVO (table 11.1 and 11.2) 40,210,213,227,278,297. These two conditions probably have different pathogenetic mechanisms, for example, a raised erythrocyte sedimentation rate (a measure of increased red cell aggregation) is common in patients with CRVO but not those with branch retinal vein occlusion ²¹². Previous investigations may therefore have under or over estimated the significance of their findings to CRVO.

Haematocrit, haematocrit corrected whole blood viscosity and plasma viscosity have all been significantly increased in patients with retinal vein occlusions both during ²²⁷ and after the acute stage ²⁷⁸ in comparison to controls. Higher whole blood viscosity has also been described in ischaemic vein occlusions than nonischaemic. Even when patients with hypertension, a history of oral contraceptive administration, diabetes or heavy smoking, were excluded similar findings were detected ²¹⁰. Increased fibrinogen ^{227,278} and erythrocyte aggregation ²⁹ or reduced red cell deformability ²¹⁰ have been detected and blamed for the increase in viscosity. Other studies have however been unable to detect any elevation of blood viscosity ^{40,297}.

Various haemostatic factors have been implicated in retinal vein occlusion, eg., increased Factor 8 which has a coagulant activity, reduced Antithrombin 3 which

table 11.1

Retinal Vein Occlusion and Blood Viscosity.

Ring 1976 44 patients with retinal vein occlusion in a controlled study 227.

He used fluorescein angiographic evidence of capillary drop-out to classify the retinal vein occlusion as ischaemic or non-ischaemic but the duration of the retinal vein occlusions is not clear from his paper. After correction for haematocrit, which was increased in the group of patients with ischaemic retinal vein occlusion, whole blood viscosity was found to be significantly increased in comparison to controls. There was a 35% increase in whole blood viscosity in the ischaemic group (at a shear rate of 0.77/sec) which was increased in comparison to patients with non ischaemic retinal vein occlusion. Plasma viscosity increased with age and was increased in the retinal vein occlusion group as a whole, but no difference was encountered between the ischaemic versus non-ischaemic groups of retinal vein occlusion.

Fibrinogen increased with age and was increased in the patients with retinal vein occlusion but was not different between ischaemic and non-ischaemic groups. Fibrinogen levels were found to relate well to plasma viscosity and may contribute to the non-Newtonian behaviour of whole blood.

Trope 1983 examined 42 patients with retinal vein occlusion after the acute stage in order to remove the possible influence of the acute thrombotic event on the rheological parameters 278. The control group was matched for systemic vascular abnormalities such as hypertension as well as for age and sex. Blood viscosity was raised in the patients with retinal vein occlusion, and was found to be 36% higher in the ischaemic group compared with the non-ischaemic group at a shear rate of 0.94/sec. Plasma viscosity was increased in this group in comparison to controls and this was closely related with fibrinogen levels. There was also a raised immunoglobulin level in the study group but there was no correlation of this with viscosity measurements.

Peduzzi 1986 performed a controlled study of 34 patients with retinal vein occlusion excluding patients with hypertension, a history of oral contraceptive administration, diabetes or heavy smoking. Increased whole blood viscosity, plasma viscosity, fibrinogen, haematocrit and reduced whole blood filterability were detected in his patients with retinal vein occlusion 220. A difference between the ischaemic and non-ischaemic groups was found for whole blood viscosity and fibrinogen levels.

Wiek 1990 examined viscosity prior to isovolemic haemodilution for treatment of retinal vein occlusion using as controls patients going for cataract and retinal detachment surgery 297. A large group of the patients were under 50 years old. In this study, the fluorescein angiographic feature of time to maximal venous filling of dye of more than or equal to 20 seconds was used for the classification of the ischaemic variant of the disorder. No significant difference in haematocrit, plasma viscosity, red cell aggregation, red cell filterability or whole blood viscosity was detected. In addition, the results for non-ischaemic or ischaemic retinal vein occlusion were similar. After isovolaemic haemodilution, haematocrit and whole blood viscosity were reduced.

Dodson 1982 also found no difference in plasma viscosity between 99 patients with retinal vein occlusion and controls despite finding a correlation between plasma viscosity and elevated serum lipid levels in the retinal vein occlusion patients 40.

Piermarocchi 1990, in a controlled study of 54 patients with branch retinal vein occlusion detected raised blood viscosity which was worse in patients with ischaemia of the retina 213.

Chabanel 1990 in 64 patients with retinal vein occlusion found an increase in mean erythrocyte aggregation compared with controls but no difference with the grade of ischaemia of the retina 29.

Table 11.2. Retinal Vein Occlusion and Haemostasis.

Trope 1983 in 42 patients with retinal vein occlusion²⁷⁸. Factor 8 antigen which is released from vascular endothelium and has a coagulant activity was increased in patients with retinal vein occlusion. Raised levels of this clotting factor have also been seen in diabetic proliferative retinopathy (Trope 1983). Antithrombin 3 which is known to be a major inhibitor of blood coagulation was significantly lower in the study group. In the patients with ischaemic retinal vein occlusion fibrinopeptide A, an indicator of activation of blood coagulation was increased. Increased beta thromboglobulin (a platelet specific protein) and reduced numbers of platelets in the ischaemic retinal vein occlusion group signified increased platelet consumption.

Dodson 1983 also found increased beta thromboglobulin as well as platelet factor 4 in retinal vein occlusion⁴⁵. Levels of beta thromboglobulin are influenced by lipoprotein cholesterol levels which are known to be increased in vein occlusion⁴⁰. The protein is released from platelet alpha granules during aggregation of platelets.*

Walsh 1977 found a 2-4% increase in platelet coagulant activities in acute retinal vein occlusion in which there was no contributory systemic or ocular disease but did not find this in a chronic group (in an uncontrolled study)²⁹⁰. He also measured levels of platelet factor 3, platelet aggregation, serotonin release by platelets and plasma coagulation and found these to be normal.

Gonder 1983 examined young patients with vein occlusion and found abnormal platelet function in the form usually of platelet coagulant hyper activity in those with associated mitral valve prolapse⁷³.

Pandolfi 1972 in an uncontrolled study of patients with retinal vein occlusion discovered increased platelet adhesiveness, factor 5, factor 8 and increased inhibitors of urokinase and plasmin. He also examined peripheral venous walls and found reduced fibrinolytic activity in these²⁰⁶.

is an inhibitor of blood coagulation and increased fibrinopeptide A which indicates the activation of blood coagulation have all been detected^{45,278}. In some studies platelet activation was increased in these patients^{45,73,206,290}.

Despite these investigations there has been no comparison of the results of blood coagulation and rheology in patients with CRVO and individuals from a population based control group. In this study, patients with CRVO (or its variant, hemiretinal vein occlusion) were examined. The patients were age matched to individuals attending population surveys²⁵⁹ to allow comparison of blood viscosity and coagulation.

11.3 Patients and Methods.

Seventy seven patients with central retinal vein occlusion and ten patients with hemiretinal vein occlusion were examined. The patients with CRVO and rheology studies were compared to a control group taken from a local population study of rheology²⁵⁹. The results were compared in a case controlled manner with each case matched for year of age. This provided 69 patients and 69 controls for comparison. The mean age of the patients and the controls was 64.2 years (SD 12.8, range 27 to 84) and the mean duration from onset of the occlusion was 3.8 months (SD 4.7). There were

39 male and 30 female patients with a mean diastolic blood pressure of 148.4 mmHg (SD 20.4) and diastolic blood pressure of 85.0 mmHg (SD 11.1).

Forty seven patients with CRVO and haemostatic variable investigations were age matched to 47 controls from another population study for comparison (Lowe et al, unpublished data). The mean age of these subjects was 61.7 years (SD 13.3, range 27 to 78 years).

Thirty five patients were age matched to 35 controls for analysis of activated protein C (mean age 61.0 years, SD 12.2). In a similar fashion twenty five patients were age matched to 25 controls for comparison of protein C and S (mean age 62.3 years, SD 11.9).

Age matching in a case controlled manner was unavailable for Von Willebrands factor and for tissue plasminogen activator and plasminogen activator inhibitor. The results from the patients over the age of 64 years were therefore compared to the results from a population study of individuals above this age (Lowe et al, unpublished data).

Twenty five patients with an ischaemic grade of retinopathy were age matched to 25 with nonischaemic CRVO. The protocol employed in the ischaemic grading has been provided in chapter 9 (table 9.1). The mean age of the ischaemic and nonischaemic CRVOs was 69.5 years (SD 9.3 years, range 51 to 85).

The patients were examined again at least one year after the onset of their occlusion for the development

of complications. Only the results from patients examined in the acute stage of the condition, ie, less than three months from onset, were analysed. The results from nine patients who went on to develop iris neovascularisation were compared to the results from twenty two patients who did not develop this complication. Three patients who presented with neovascularisation and one patient who developed retinal neovascularisation were excluded.

Blood Sampling

15 mls of venous blood was sampled from an antecubital vein through a 21 gauge butterfly needle after minimal use of a tourniquet. Five mls of blood was anticoagulated with dipotassium edetate (K_2EDTA , 1.5mg/ml) for viscosity examination which was performed within four hours of sampling. 9 mls of blood was placed directly into a tube with 1ml trisodium citrate (0.109 M) and within one hour of the sampling centrifuged at 15,000 rpm (25,000 g) for ten minutes. The plasma was then aliquoted into seven separate sample tubes and stored at -30 degrees Celsius for 48 hrs. The samples were then transported in ice to a -70 degree Celsius freezer. In a group of 20 patients examined within one month of the onset of the occlusion the rheology samples were repeated at 6 months and at 1 year.

Blood Rheology

Viscosity variables were measured as previously described in chapter 6.

Haemostatic Variables

Fibrinogen was measured by the Clauss method on a Coag-A-mate X2 coagulometer using the manufacturer's reagents and international standard (Organon Teknika, Cambridge, UK). Clotting factors VII, VIII and IX were recorded by one-stage clotting methods on an ACL300 coagulometer similarly employing the manufacturer's reagents and international standards (Instrumentation laboratories, Warrington, UK). Antithrombin III was measured by the manufacturer's chromogenic assay in the same instrument. Plasminogen activator inhibitor activity was measured chromogenically (Quadracel, Epsom, Surrey, UK) and tissue plasminogen activator antigen measured by an ELISA technique (Biopool, Stockholm, Sweden). These two factors were assessed only on the patients with CRVO as was von Willebrand factor antigen which was recorded using an ELISA technique (Dako ltd., High Wycombe, Bucks, UK). Activated protein C was also measured ^{14,204} (ACL 300R, Instrumentation laboratories, Warrington, UK).

Statistical Analysis

The results were compared by 2 tailed students T-test and analysis of covariance (with the covariant the age

of the patient) where appropriate, 95% confidence limits are provided.

11.4 Results

Blood Viscosity - whole group (Table 11.3).

The corrected blood viscosity was higher in the patients with CRVO (mean 3.44 mPa s, SD 0.42, upper confidence limit 3.55 and lower 3.33), than the controls (mean 3.24 mPa s, SD 0.41 upper confidence limit 3.34 and lower 3.12, $p=0.007$, figure 11.1). The relative blood viscosity was also higher in the patients with CRVO (mean 2.57 mPa s, SD 0.24, upper confidence limit 2.63 and lower 2.51) than the controls (mean 2.42 mPa s, SD 0.30, upper confidence limit 2.50 and lower 2.35, $p=0.005$, figure 11.2).

Haemostatic Variables - whole group (table 11.4).

Antithrombin III was significantly higher in the patients (mean 101.8 iu/dl, SD 13.0, upper confidence limit 107.0 and lower 98.9) than the controls (mean 95.1 iu/dl, SD 11.5, upper limit 99.1 and lower 92.5, $p=0.02$).

VWF was significantly higher in the patients with CRVO (mean 141 iu/dl, SD 56, upper confidence limit 157, lower 126) than in the control population (mean 126 iu/dl, SD 49, upper limit 134 and lower 119, $p=0.05$),

Table 11.3

	Controls (n=69) mean (SD)	CRVO (n=69)	p value
Whole Blood Viscosity (mPa s)	3.19 (0.50)	3.35 (0.57)	0.23
Plasma Viscosity (mPa s)	1.34 (0.07)	1.35 (0.12)	0.91
Haematocrit (%)	43.9 (4.16)	43.6 (4.60)	0.72
Red Cell Aggregation (arbitrary units)	4.37 (1.09)	4.15 (1.20)	0.37
Corrected Blood Viscosity (mPa s)	3.24 (0.41)	3.44 (0.42)	0.007
Relative Blood Viscosity	2.42 (0.30)	2.57 (0.24)	0.005

Table 11.3. The results of the measures of blood viscosity (mean and SDs) in the patients with CRVO and the controls showing that the haematocrit corrected and relative blood viscosities are higher in the patients ($p=0.03$ and $p=0.015$, respectively).

Corrected Blood Viscosity

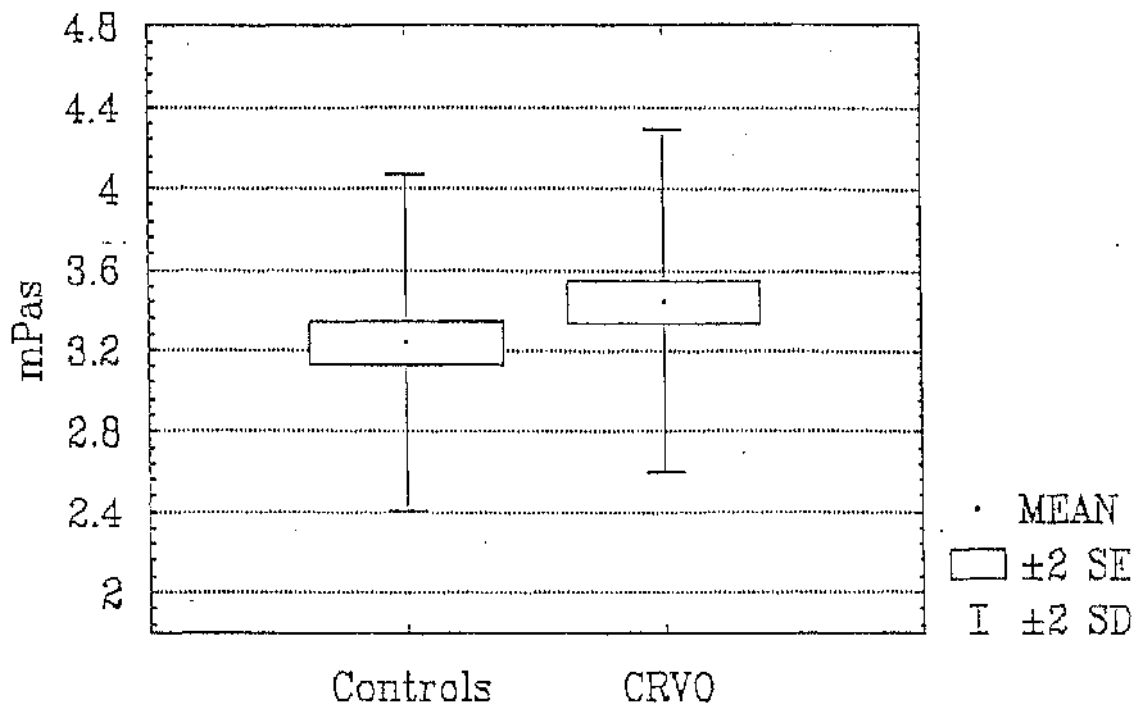


Figure 11.1. The mean haematocrit corrected blood viscosities from the patients with CRVO and the controls are shown (including $2 \times \text{SD}$ and $2 \times \text{SE}$).

Relative Blood Viscosity

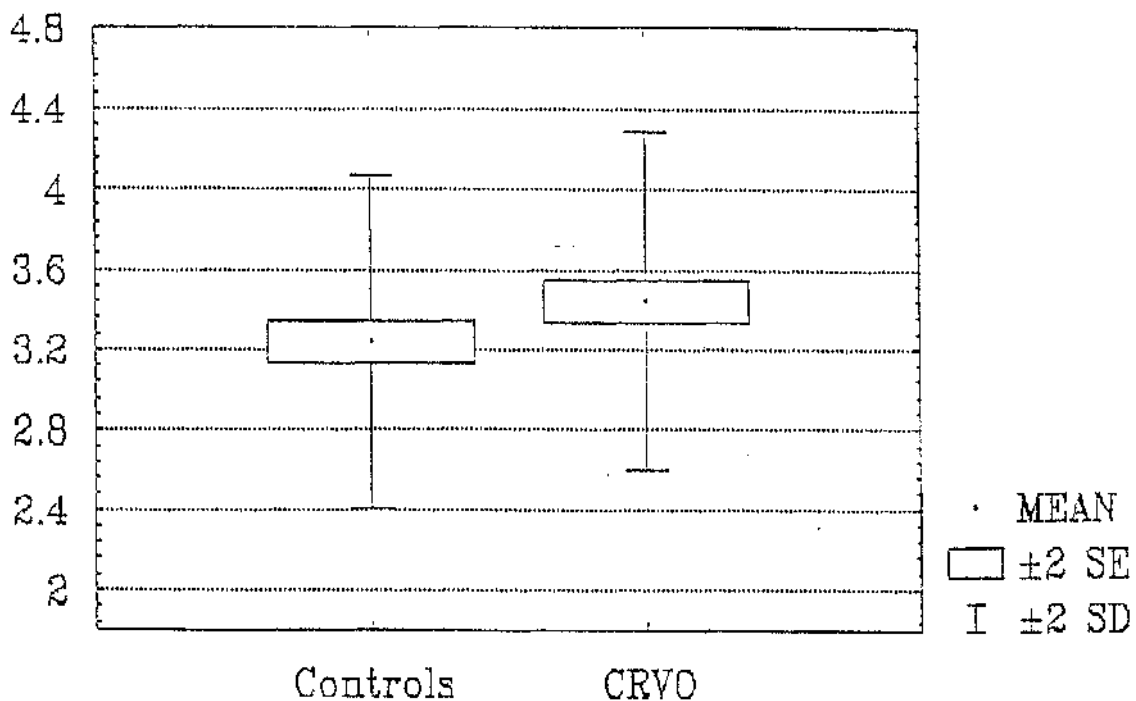


Figure 11.2. The mean relative blood viscosities from the patients with CRVO and the controls are shown (including the $2 \times \text{SD}$ and $2 \times \text{SE}$).

Table 11.4

	Controls (n=47) mean (SD)	CRVO (n=47)	p value
Factor VII (iu/dl)	113.4 (28.3)	112.9 (27.6)	0.93
Factor VIII (iu/dl)	142.4 (50.3)	141.4 (60.1)	0.59
Factor IX (iu/dl)	128.2 (44.8)	136.3 (41.9)	0.30
Antithrombin III (iu/dl)	95.1 (11.5)	101.8 (13.0)	0.02
Fibrinogen (g/l)	2.91 (0.91)	3.10 (0.78)	0.15
Von Willebrand's Factor 126 (49)		142 (56)	0.05
Tissue Plasminogen Activator 8.3 (3.3)		9.8 (14.8)	0.43
Plasminogen Activator Inhibitor 75.7 (32.8)		95.8 (35.3)	0.004
Protein C (n=25) 110 (38)		127 (23)	0.055
Protein S 142 (18)		135 (17)	0.15
APC (n=35) 2.85 (0.50)		2.62 (0.50)	0.05

Table 11.4. The results of the comparison of haemostatic variables in the patients with CRVO and the controls showing an increase in mean antithrombin III, von Willebrands factor and plasminogen activator inhibitor in the patients with CRVO and reduced activated protein C.

as was PAI (CRVO patients mean 96 iu/dl, SD 35, upper limit 107 and lower 84 and controls mean 76 iu/dl, SD 33, upper limit 83 and lower 68, $p < 0.0001$). APC was higher in the controls (mean 2.85, SD 0.5, upper limit 3.01 and lower 2.69) than in the patients (mean 2.62, SD 0.5, upper 2.78 and lower 2.46, $p = 0.05$).

Retinal Ischaemia

The plasma viscosity was lower in the ischaemic group (mean 1.31 mPa s, SD 0.07, upper confidence limit 1.34 and lower 1.28) than in the nonischaemic patients (mean 1.38 mPas, SD 0.11, upper confidence limit 1.43 and lower 1.33, $p = 0.03$). Protein S was significantly higher in the non ischaemic group (mean 140, SD 22.5, upper limit 151, lower 129) than the ischaemic (123, SD 15.9, upper 135 and lower 112, $p = 0.05$). No difference was found in any of the other parameters (table 11.5 and 11.6).

The Development of Iris Neovascularisation

Patients who were examined in the acute stage of the condition and who went on to develop iris neovascularisation had significantly lower factor VII (mean 95.7 iu/dl, SD 16.3, upper limit 114 and lower 77), Antithrombin III (92.8 iu/dl, SD 12.1, upper limit 109 and lower 76) and tissue plasminogen activator (4.62 iu/dl, SD 2.0, upper 7.5 and lower 1.7) compared to those who did not develop neovascular complications,

Table 11.5

	Non Ischaemic (n=25) mean (SD)	Ischaemic (n=25)	p value
Whole Blood Viscosity (mPa s)	3.49 (0.76)	3.26 (0.52)	0.34
Plasma Viscosity (mPa s)	1.38 (0.11)	1.31 (0.07)	0.03
Haematocrit (%)	43.8 (5.05)	43.9 (4.70)	0.46
Red Cell Aggregation (arbitrary units)	4.16 (1.14)	4.54 (1.12)	0.22
Corrected Blood Viscosity (mPa s)	3.54 (0.49)	3.33 (0.41)	0.13
Relative Blood Viscosity	2.57 (0.26)	2.53 (0.27)	0.69

Table 11.5, The results of blood viscosity measurements for those patients with retinal ischaemia and those without. Only the plasma viscosity was significantly different being higher in the nonischaemic group (p=0.02).

Table 11.6

	Non Ischaemic (n=18)	Ischaemic (n=18) mean (SD)	p value
Factor VII (iu/dl)	118.9 (17.9)	121.1 (31.6)	0.86
Factor VIII (iu/dl)	141.6 (37.4)	159.8 (85.9)	0.96
Factor IX (iu/dl)	142.0 (29.5)	160.1 (37.6)	0.13
Antithrombin III (iu/dl)	106.0 (10.1)	103.1 (14.2)	0.69
Fibrinogen (g/l)	3.28 (0.87)	3.26 (0.80)	1.00
Tissue Plasminogen Activator (iu/dl)	12.7 (21.8)	7.3 (2.8)	0.95
Plasminogen Activator Inhibitor (iu/dl)	89.1 (25.4)	80.1 (28.3)	0.44
Von Willebrand's Factor (iu/dl)	97.8 (30.2)	105.7 (46.2)	0.88
Protein C	127 (26)	121 (24)	0.56
Protein S	140 (22)	123 (16)	0.05
APC	2.6 (0.4)	2.4 (0.5)	0.34

Table 11.6. The haemostatic variables showing a significant difference between the values for the patients with ischaemia of the retina and those with no ischaemia only for protein S.

factor VII (125.8 iu/dl, SD 20.8, upper limit 136 and lower 116), Antithrombin III (107.4 iu/dl, SD 9.9, upper limit 113 and lower 102), and tissue plasminogen activator (7.25 iu/dl, SD 2.5, upper 8.5 and lower 6.0). The results are shown on table 11.7. There was no difference in blood viscosity parameters.

Serial Viscosities in Patients Examined Within Three Months of Onset.

At 6 months only haematocrit was lower than the result at onset ($p=0.01$). At one year however, whole blood viscosity, haematocrit-corrected blood viscosity and relative blood viscosity were all lower at one year after the occlusion than at the onset (all, $p<0.05$, figures 11.3 and 11.4). Haematocrit corrected blood viscosity was also lower at 1 year than 6 months ($p<0.05$).

11.5 Discussion

Blood Viscosity

In this study, both haematocrit-corrected and relative blood viscosity were higher in patients with CRVO than in the age matched control population, but no significant elevation was detected in erythrocyte aggregation or fibrinogen. These findings confirm the results of previous studies which have indicated that

Table 11.7.

n	No Rubeosis	Rubeosis	p value
	17 mean (SD)	7	
Factor VII (iu/dl)	125.8 (20.8)	95.7 (16.3)	0.005
Factor VIII (iu/dl)	152.9 (53.0)	138.3 (29.5)	0.50
Factor IX (iu/dl)	142.7 (33.3)	118.6 (29.0)	0.15
Antithrombin III (iu/dl)	107.4 (9.9)	92.8 (12.1)	0.04
Fibrinogen (g/l)	3.26 (0.84)	3.04 (0.68)	0.48
Tissue Plasminogen Activator (iu/dl)	7.25 (2.5)	4.62 (2.0)	0.03
Plasminogen Activator Inhibitor (iu/dl)	92.1 (29.4)	91.0 (17.1)	0.61
Von Willebrand Factor (iu/dl)	105.8 (57.9)	117.7 (24.6)	0.30
Protein C	126 (25)	106 (34)	0.21
Protein S	141 (21)	130 (30)	0.47
APC	2.53 (0.53)	2.94 (0.35)	0.10

Table 11.7. The values obtained for the haemostatic variables are shown for those patients examined within three months who did or did not develop iris neovascularisation by one year of follow up.

Corrected Blood Viscosity

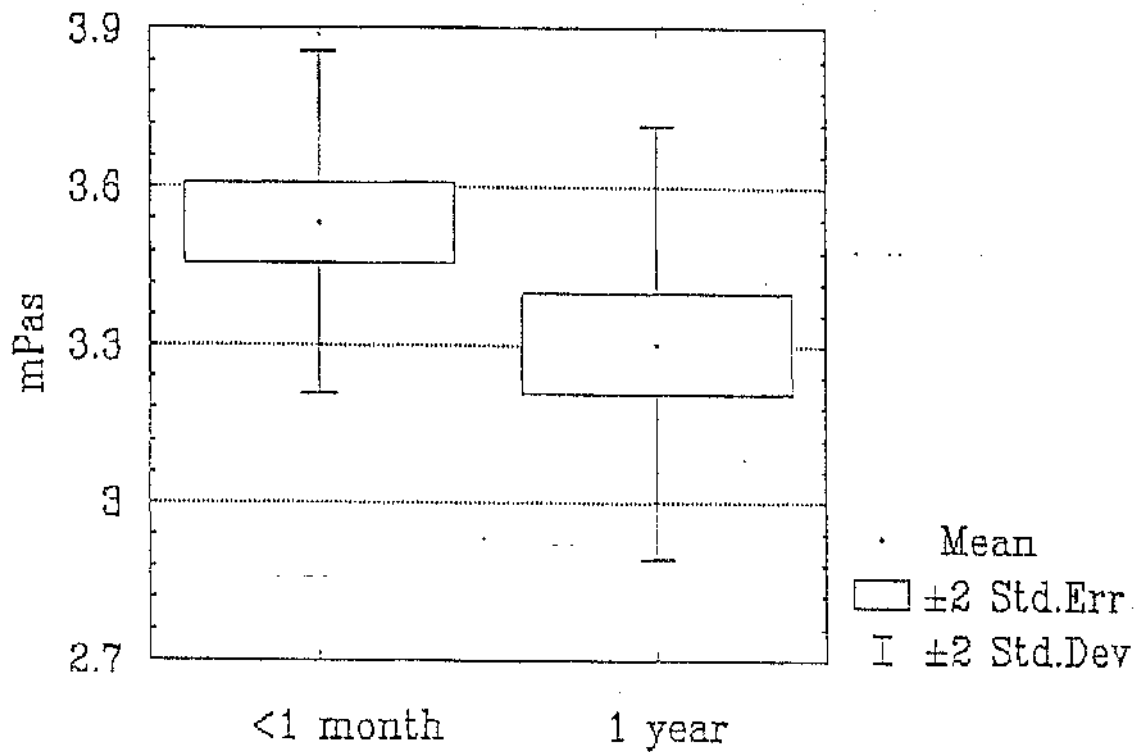


Figure 11.3. The haematocrit-corrected blood viscosities in patients examined within one month of the onset of venous obstruction are shown at presentation and after one year of follow up.

Relative Blood Viscosity

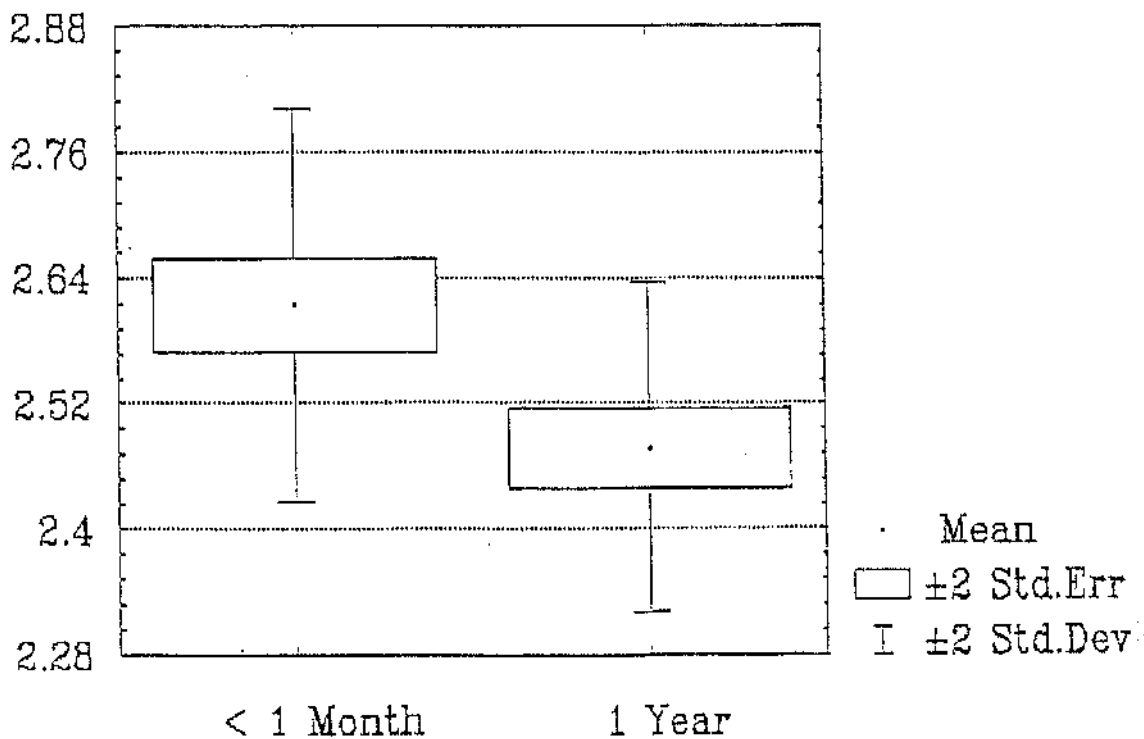


Figure 11.4. The relative blood viscosities in patients examined within 1 month of the onset of venous occlusion are shown at presentation and after one year of follow up.

patients may be at risk of retinal venous occlusion because of the presence of systemic rheological abnormalities. The results from this study also suggest that cellular factors, ie., cellular deformability, were most important because relative blood viscosity was higher in these patients. In explanation, first haematocrit corrected blood viscosity was calculated to remove the contribution of haematocrit on blood viscosity and secondly relative blood viscosity was calculated to negate the influence of plasma viscosity. Relative blood viscosity therefore provides an indirect measure of the viscosity resultant from cellular factors in the blood such as deformability and aggregation. As there was no difference in red cell aggregation between the two groups blood cell deformability was likely to be the main cause of the increased viscosity in these patients.

It would appear that in CRVO there is a higher viscosity at the time of onset of the occlusion and that the viscosity slowly drops over the year following. It is possible that the occlusion occurred at a time of raised viscosity for some as yet undetermined reason, or that general medical advice after the presentation of the patient, eg., on reducing blood pressure or lipid levels, resulted in a reduction in viscosity.

Significantly higher whole blood viscosities in the ischaemic form of retinal vein occlusion (mixed retinal

vein occlusion) than nonischaemic have been described previously ^{210,213,227,278}. Indeed, stagnation of blood flow in the microcirculation secondary to the elevated viscosity may explain why capillary nonperfusion is seen on fluorescein angiography in ischaemic cases. The force required to induce movement in static blood (yield stress) has also been found to be significantly elevated in the blood of patients with ischaemic vein occlusions and is evidence of this increased tendency to stagnation of blood flow ²²⁷. In this study viscosity does not appear to determine whether ischaemia occurred or not. Indeed a relatively lower plasma viscosity was found in the patients with ischaemic features.

Haemostasis

The production of a blood clot first involves aggregation of platelets upon a site of damaged vascular endothelium, followed by the stabilisation and extension of this aggregate by fibrin, which is converted from the soluble protein fibrinogen via the intrinsic and extrinsic cascade reactions of various clotting factors. This thrombotic mechanism is balanced by factors which prevent formation of the clot, eg., Antithrombin III, protein C, protein S and by the fibrinolytic system which converts plasminogen to plasmin which in turn acts to lyse fibrin and

fibrinogen. The fibrinolytic system involves the interaction of factors such as tissue plasminogen activator (increasing fibrinolysis) and plasminogen activator inhibitor (reducing fibrinolysis). In some circumstances an imbalance of these systems help to cause thrombosis.

The role of increased coagulation activity and reduced fibrinolysis in CRVO is as yet unknown. Histological studies suggest that thrombus formation occurs in the retinal vein, therefore the haemostatic systems may be important ^{80,225}. However, most of the cases that have been reported have had rubeotic glaucoma and the few who have been examined in the acute stage of the disorder without rubeosis have all presented atypically. Deficiencies of antithrombin III, protein C and protein S have been detected in a longstanding mixed group of retinal vein occlusions signifying an increased risk of thrombosis ²⁷⁸. Also raised coagulation factor VIII has been found which signifies increased coagulant activity, and elevated fibrinopeptide A levels have provided a measure of increased activation of coagulation ²⁷⁸.

In this study, an increase in the antithrombin III level in the patients with CRVO was observed. This is in contradiction to the deficiency of antithrombin III which was detected in longstanding retinal vein occlusions in a previous study ²⁷⁸. It may be that the antithrombin III levels were reduced in the previous

study because of the inclusion of patients with branch vein occlusion. Alternatively it has been suggested that an increase in antithrombin III may sometimes occur, possibly as a compensatory reaction to increased coagulation factors because both low and high antithrombin III levels are predictive of ischaemic heart disease ¹⁹².

In contrast those patients who subsequently developed iris neovascularisation did show changes which suggest a tendency to thrombosis and impaired fibrinolysis (table 11.7). The lower levels of antithrombin III in these patients signifies an increased tendency to the formation of thrombus. A reduction in fibrinolytic activity was evident in these patients from lower levels of tissue plasminogen activator than controls (in the presence of unchanged plasminogen activator inhibitor), indicating a relative inability to lyse thrombus. Defective fibrinolysis has been associated before with new vessel formation ²⁰⁹. The patients with rubeosis iridis also had lower levels of coagulation factor VII and a trend to lower factor IX (table 11.7), changes which may partly balance the prothrombotic effects of low antithrombin III and tissue plasminogen activator. Although the patients classified as ischaemic had lower protein S (an anticoagulant nonenzymatic cofactor for Protein C) no difference was detected in those patients who went on

to develop rubeosis.

Low activated protein C (APC resistance) has recently been described in patients with thrombotic tendencies¹⁴. Inheritance of the deficiency is thought to be considerably more common in the general population than deficiencies of Protein C, S and antithrombin III. In this study 12.5% of the patients with CRVO had APC resistance compared with 5% of the controls.

A Pathogenetic Mechanism for CRVO

The results suggest that increased viscosity produces a risk of CRVO and that abnormalities of haemostasis (by increasing the chance of thrombus formation) are associated with the development of iris neovascularisation. Ring has previously suggested that a "rheological obstruction" may occur in patients with retinal vein occlusion²²⁷. These results imply that viscosity produces stasis of blood in the vein without the formation of thrombus in most patients. This would explain why reduction of blood viscosity (isovolaemic haemodilution) in the treatment of CRVO aids the recovery of vision whilst anticoagulation has been unsuccessful²⁸². Stasis of blood flow in some "at risk" individuals may then result in the development of thrombosis within the vein, further reducing blood flow. The thrombus persists in patients with a deficient fibrinolytic system, chronically reducing their retinal blood flow and thereby resulting in the

development of neovascular complications. The risk of this complication is reduced by the use of streptokinase to break down the thrombus ¹³⁷ but unfortunately this agent has also produced vitreous haemorrhage in some patients and has had little overall effect upon visual recovery.

In summary our results suggest that raised blood viscosity (from reduced cell deformability) is present in patients with central retinal vein occlusion and may cause a reduction or stasis of blood flow in the vein. Those patients who develop neovascular complications have abnormalities of haemostasis and may develop complications because thrombus formation in the vein further reduces their retinal blood flow.

12 Chapter 12.

THE INTERRELATIONSHIP OF BLOOD VISCOSITY AND BLOOD FLOW IN CENTRAL RETINAL VEIN OCCLUSION.

12.1 Summary

In normal individuals there is a compensation for increased blood viscosity by reduction of peripheral resistance. Having discovered a pattern of blood viscosity elevation in the patients with CRVO, the relationship between the blood viscosity and the orbital velocities was investigated with particular relevance to the unaffected fellow eyes of these patients. Increased viscosity in these cases resulted in reduced blood velocities without any reduction in the peripheral resistance. Whereas normal healthy individuals compensate for increased viscosity, patients with CRVO appear to be unable to do so resulting in a risk of occlusion of the central retinal vein.

12.2 Introduction.

The blood flow in a vessel is dependent upon a number of parameters including the diameter and length of the vessel, the perfusion pressure and the viscosity of the blood. In turn, viscosity is altered by a complex interaction of the cellular and plasma components of the blood (see chapter 7). Abnormalities of blood flow and blood rheology in patients with the condition of CRVO have been demonstrated in chapters 9 and 11 respectively. Also a relationship has been shown to exist between blood viscosity and blood flow in normal individuals in chapter 7. In this chapter the relationships between these two factors were investigated in the patients with CRVO.

Patients and methods.

The patients affected by CRVO were examined by colour Doppler imaging and had blood sampling for rheology and coagulation examination within 2 hours of each other. Those patients examined within 1 month of onset of the occlusion of the central retinal vein were also examined by CDI and rheology at one year after onset. The results of colour Doppler imaging and blood rheology were analysed by multiple linear regression analysis allowing a correction for age (and also systolic blood pressure for PSV in the ophthalmic

artery, significance taken as $p < 0.05$). The results for both the fellow eye and the eye affected by the occlusion were examined.

12.3 Results.

Fellow Eye

Correlations were discovered between the PSV in the ophthalmic artery and plasma viscosity ($b = -0.35$), whole blood viscosity ($b = -0.42$) and haematocrit corrected blood viscosity ($b = -0.42$), and also red cell aggregation ($b = -0.34$, figures 12.1 to 12.4). Only corrected blood viscosity varied with EDV in this artery ($b = -0.30$, figure 12.3). Relative blood viscosity was weakly negatively correlated with PSV ($b = -0.28$) and Vmax ($b = -0.29$) in the central retinal artery and vein respectively (figure 12.5). Haematocrit was negatively correlated with the resistive index in the central retinal artery ($b = -0.29$) but this appeared to be influenced by one patient with anaemia and a low haematocrit.

Eyes with Central Retinal Vein Occlusion.

Red cell aggregation negatively correlated with the Vmin in the central retinal vein ($b = -0.29$, figure 12.6). Pulsatility index in the central retinal vein negatively correlated with the relative blood viscosity

Ophthalmic Artery Whole Blood Viscosity

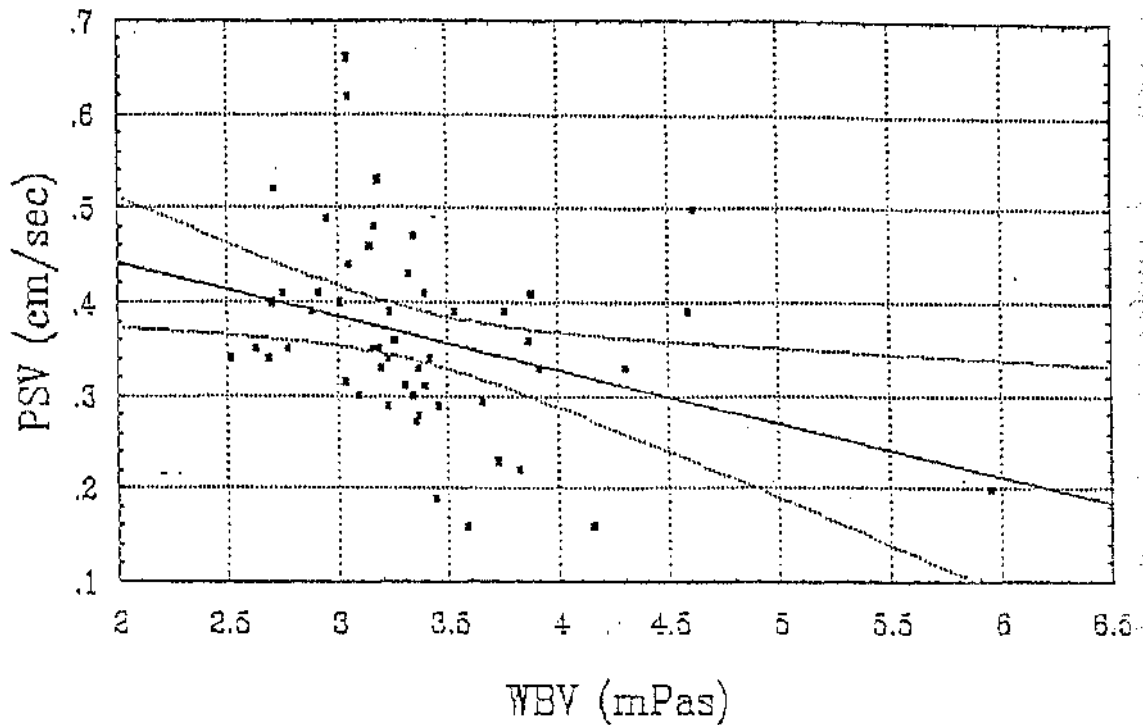


Figure 12.1. A scattergram of the PSV in the ophthalmic artery of fellow unaffected eyes of patients with CRVO and the whole blood viscosity showing a negative correlation (a linear regression line and 95% confidence levels are shown).

Ophthalmic Artery Plasma Viscosity

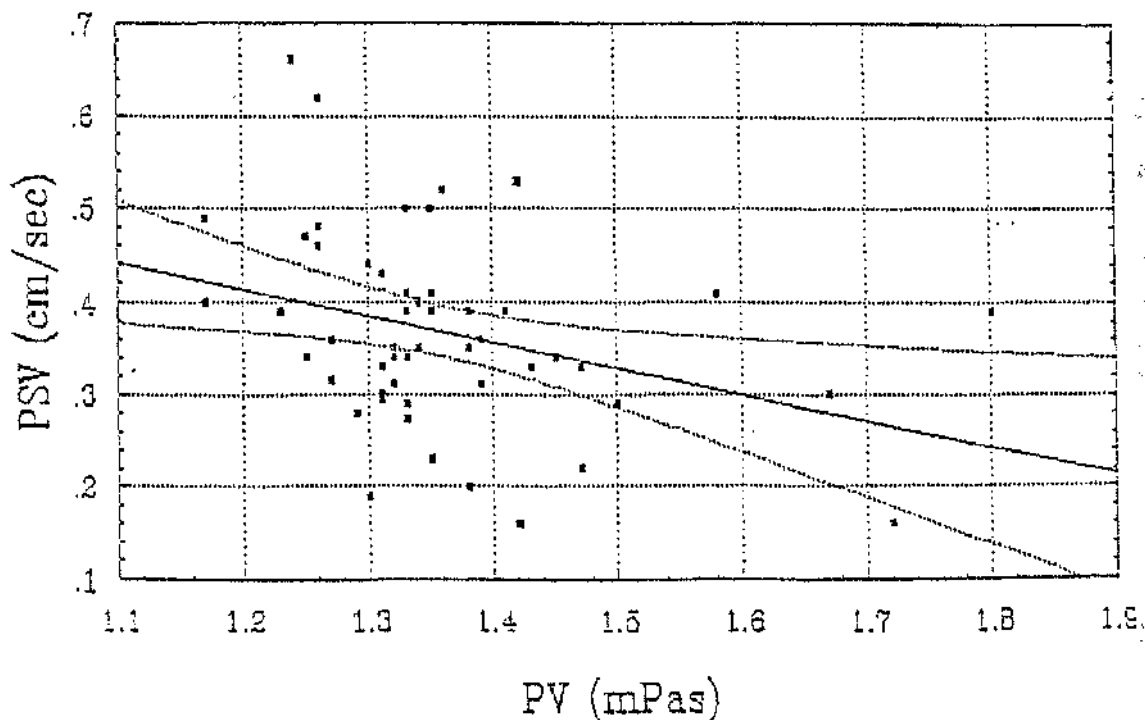


Figure 12.2. A scattergram showing the relationship between the PSV in the ophthalmic artery in unaffected fellow eyes and the plasma viscosity showing a negative correlation (a linear regression line and 95% confidence levels are shown).

Ophthalmic Artery Velocities v Viscosity

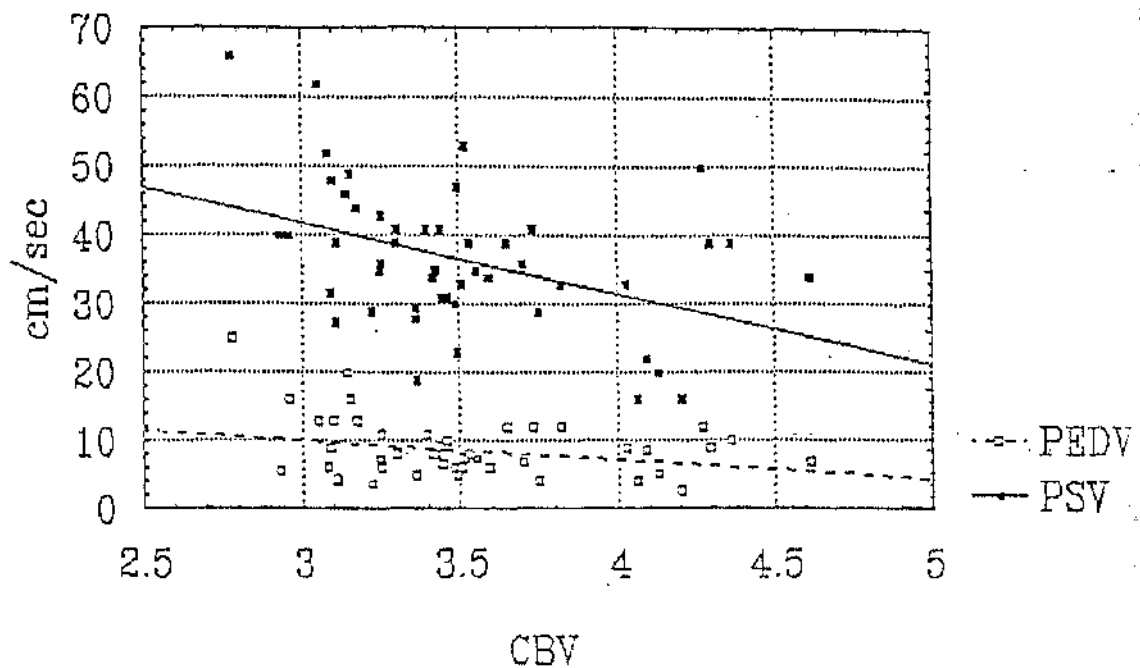


Figure 12.3. A scattergram showing the relationship between the PSV and EDV in the ophthalmic artery of unaffected fellow eyes and the haematocrit corrected blood viscosity (linear regression lines are provided).

Ophthalmic Artery Red Cell Aggregation

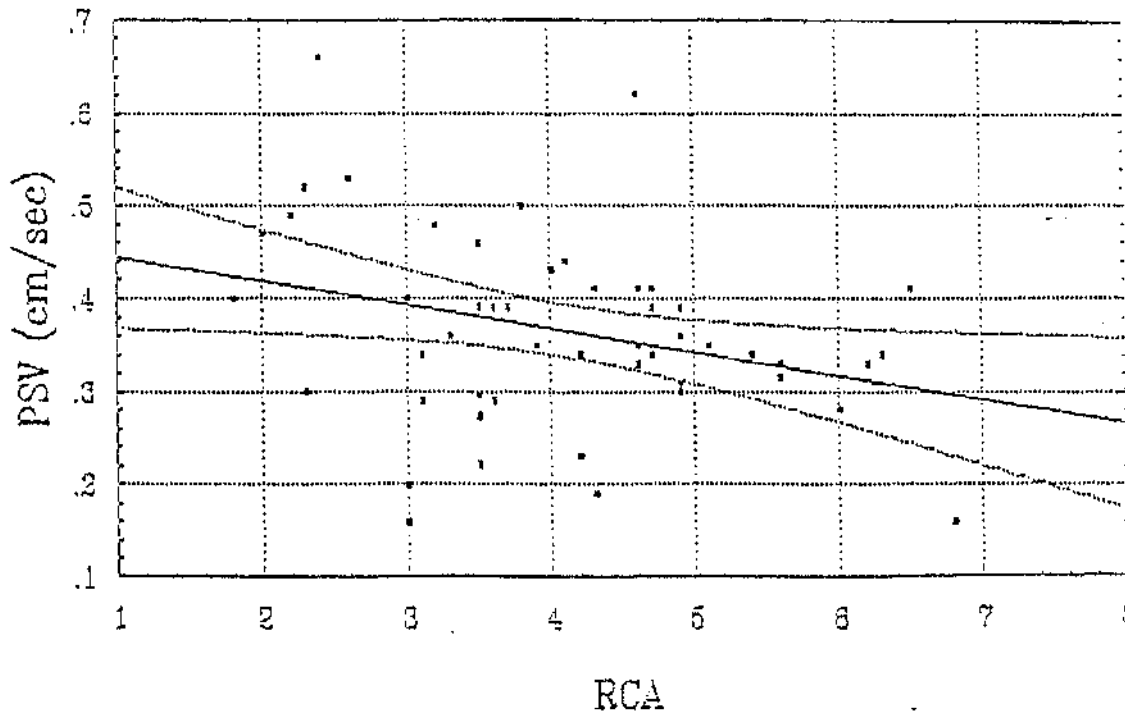


Figure 12.4. A scattergram of the PSV in the ophthalmic artery of unaffected fellow eyes and red cell aggregation showing a negative correlation (a linear regression line and 95% confidence levels are shown).

Retinal Blood Velocities (PSV and Vmax) v Viscosity

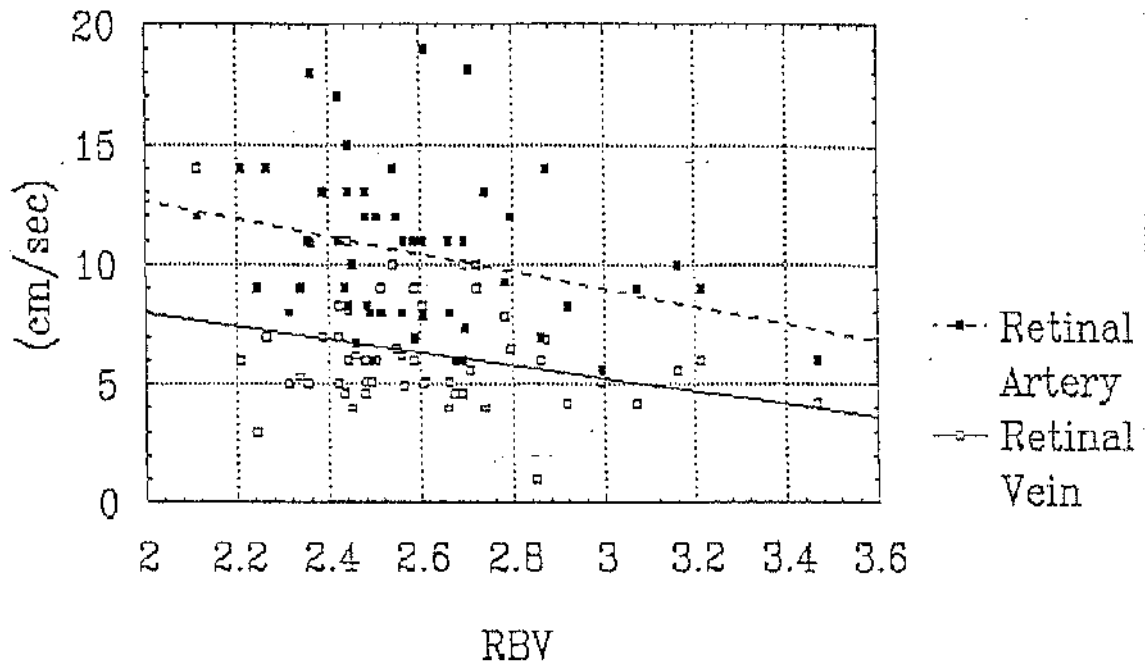


Figure 12.5. A scattergram of the relative blood viscosity and the PSV in the central retinal artery and Vmax in the vein of unaffected fellow eyes respectively showing a reduction in the velocities with elevated viscosity (linear regression lines are provided).

Red Cell Aggregation and Venous Velocity

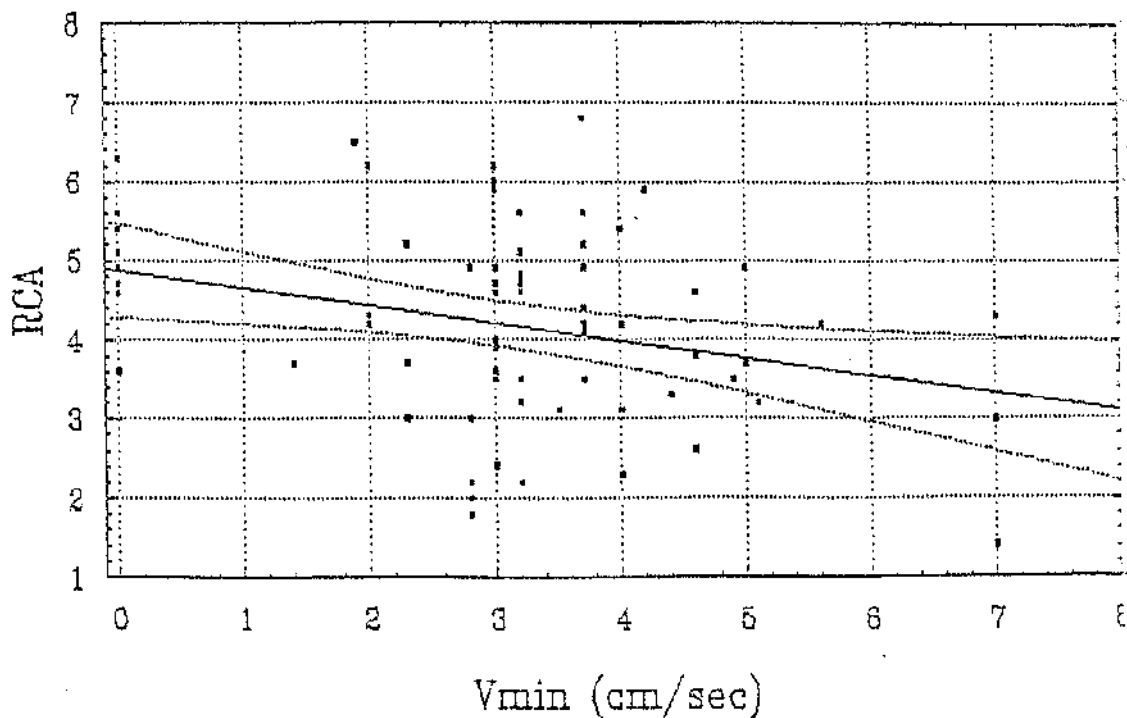


Figure 12.6. A scattergram of the Vmin in the central retinal vein of eyes affected by CRVO and red cell aggregation showing a negative correlation (a linear regression line and 95% confidence levels are shown).

($b=-0.27$) and positively with the plasma viscosity, ($b=0.33$, figures 12.7 and 12.8).

12.4 Discussion

As with the control population a relationship was discovered between blood rheology and the Doppler measurements in the orbital blood vessels. The pattern of the correlations was however different. Whereas in the normal eyes there was no correlation between the velocities in the ophthalmic artery and the viscosity measurements, in the fellow eyes of patients with CRVO whole blood and plasma viscosity, haematocrit corrected blood viscosity, haematocrit and red cell aggregation all correlated negatively with the velocities from this vessel. This may signify a lack of ability of the microcirculation of these patients to compensate for raised viscosity.

In the smaller blood vessels of the retinal circulation relative blood viscosity negatively correlated with the blood velocity. In contrast in the normal population the velocities were unaffected by any of the measures of viscosity. Again in the normal individuals dilation of the peripheral blood vessels may compensate for increased blood viscosity whereas the reduction in the velocities in the patients may signify an inability to make compensatory adjustments.

In the colour Doppler examination of the eyes affected by the occlusion, the blood velocities in the central

Venous Pulsatility and Relative Blood Viscosity

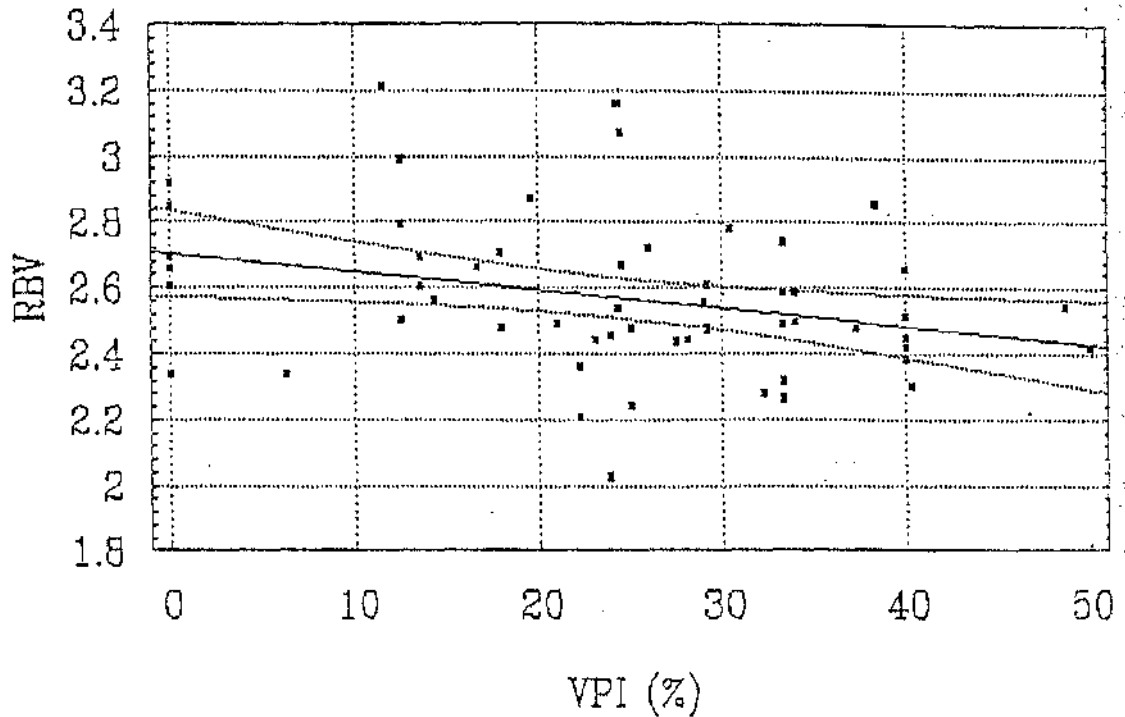


Figure 12.7. A scattergram of the venous pulsatility index in the central retinal vein of eyes affected by CRVO and the relative blood viscosity showing a negative correlation (a linear regression line and 95% confidence levels are shown).

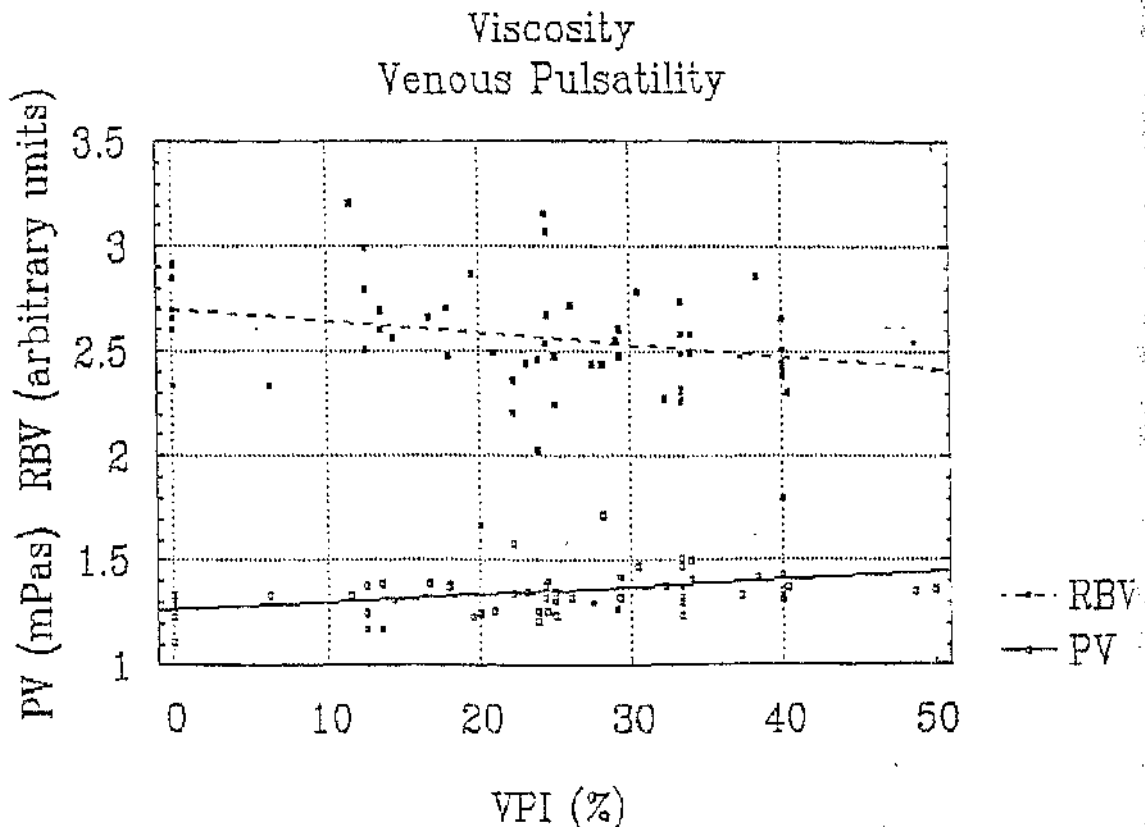


Figure 12.8. The interaction of the plasma viscosity and the relative blood viscosity upon the pulsatility index in the vein of eyes affected by CRVO is shown, i.e., the pulsatility negatively correlated with relative blood viscosity but positively correlated with the plasma viscosity (linear regression lines are provided).

retinal vein were particularly reduced in those patients who developed iris neovascularisation. In this analysis red cell aggregation was negatively correlated with the V_{min} and may therefore be important in reducing the blood flow in the vein thereby inducing a risk of neovascularisation. Red cell aggregation affects the viscosity more at low shear rates (low blood velocity) and therefore it is not surprising that the low venous velocities in the occluded circulations were reduced further by this factor.

In chapter 9 it was suggested that the pulsatility of flow in the vein may be important in avoiding stasis of blood flow. It was therefore interesting to observe that the venous pulsatility index was negatively correlated with relative blood viscosity but positively with plasma viscosity. The calculation of relative blood viscosity corrects for the plasma viscosity and provides a measure of the red cell deformability which therefore may have caused reduced pulsatility in the vein. Why then is increased plasma viscosity associated with increased venous blood pulsatility? This can be explained by the fact that increased plasma viscosity causes reduced red cell deformation and therefore increased relative blood viscosity. This is because a cell which is bathed in a highly viscous fluid is less able to change its shape than a cell in low viscosity fluid.

The deformability of blood cells therefore may be a determinant of the pulsatility of flow in the central retinal vein in these patients. This is in accordance with the results from chapter 7 and 11 in which the relative blood viscosity was shown to reduce the pulsatility index in the vein (in normal individuals) and to be raised in patients with CRVO. The relative blood viscosity and therefore red cell deformability appears to be of predominant importance in the production of CRVO whereas the risk of iris neovascularisation depends upon red cell aggregation and coagulation abnormalities which may reduce the blood flow further.

**DISCUSSION OF THE RESULTS OF THE HAEMODYNAMIC STUDIES
OF THE EYE AND SUGGESTIONS FOR FUTURE INVESTIGATIONS**

In these studies a new method has been introduced for the assessment of blood flow in the eye, namely colour Doppler imaging, which has provided a reproducible means of assessing the pulsatile blood velocities in the ophthalmic artery, central retinal artery and vein. The velocities obtained are affected by certain systemic factors such as age, posture, systemic blood pressure and cigarette smoking and other factors such as intra-ocular pressure elevation, all of which should be controlled for in future studies.

The technique was employed in the examination of a cohort of patients suffering from central retinal vein occlusion. In these patients evidence of increased resistance to blood flow was found in the ophthalmic artery of the fellow unaffected eyes. In addition a reduction in the pulsatile component of the flow in the central retinal vein was discovered in these eyes compared to controls which may suggest a risk of occlusion in these patients.

In those eyes with central retinal vein occlusion reduced velocities were found in the retinal circulation particularly in the central retinal vein and especially low velocities were found in patients in whom iris neovascularisation subsequently developed.

Examination of receiver operator characteristic curves showed that a minimum velocity in the vein of less than 3.0 cm/sec provided a highly predictive value for the detection of patients who developed this complication. For patients examined within three months from onset of the occlusion the sensitivity of 75% and specificity of 86% for prediction of iris neovascularisation by CDI was superior to the results obtained for fluorescein angiography (sensitivity of 60% and specificity of 67%). In addition, CDI was successfully applied to the investigation of all of these patients whereas angiography was unassessable in 20% of the patients because of opacities in the media, retinal haemorrhages or poor agreement amongst observers.

To determine the cause of the haemodynamic abnormalities found in CRVO, blood viscosity and haemostasis were also assessed. As a group the patients with CRVO had raised blood viscosity compared with age matched normal individuals. In particular increased red cell deformability appeared to be most influential in the association with occlusion. The group of patients who developed iris neovascularisation had a relatively increased tendency to produce thrombus and a reduced capability to lyse fibrin. Consequently, I have proposed that thrombosis occurs only in at risk individuals who suffer a "functional" or "rheological" blockage to flow associated with elevated blood

viscosity.

The interrelationship between measures of blood viscosity and the orbital blood velocities suggests that in normal individuals compensatory adjustments in the peripheral resistance to flow occur to maintain the blood flow (figure 13.1) because as the viscosity rises the peripheral resistance falls (perhaps from vasodilation) and the velocities remain stable. In the patients with CRVO, however, raised viscosity instead of being associated with a reduction in the resistance to flow was associated with a reduction in the blood velocities in the orbital vessels (figure 13.2). Red cell aggregation in the low flow venous circulation of eyes with CRVO negatively correlated with the blood velocities and may be important in further reducing the flow in the compromised circulation (figure 13.3).

Not only is there an increase in the blood viscosity in central retinal vein occlusion but there is also an apparent inability to compensate for changes in blood viscosity. This may result in a reduction of blood flow with a resultant formation of thrombosis in at risk individuals.

Controls

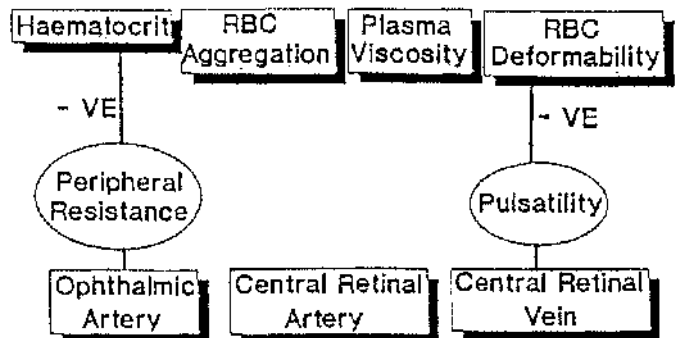


Figure 13.1. The influence of the various measures of viscosity upon the Doppler indices from the control population showing that there is a predominant effect upon reducing peripheral resistance in the ophthalmic artery and pulsatile flow in the central retinal vein (+ve = positive correlation, -ve = negative correlation).

Fellow Eyes of CRVO

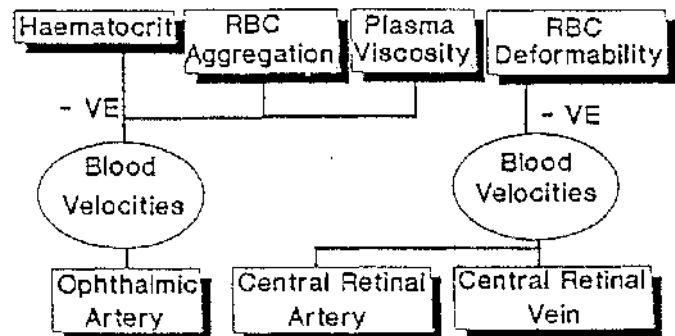


Figure 13.2. Blood viscosity shows negative correlations with the blood velocities from the arteries of the unaffected fellow eyes of patients with CRVO.

CRVO

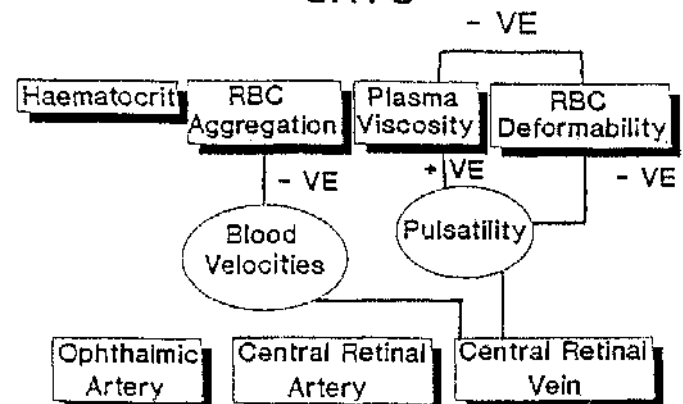


Figure 13.3. The blood velocities in the central retinal vein of eyes with CRVO demonstrated a negative correlation with red cell aggregation. The pulsatility of flow in the vein was negatively correlated with red cell deformability.

Future Studies

These studies have aided the planning of future investigations of blood flow in the eye. An area of interest in the normal physiology of the eye is the determination of the source of the pulsatile blood flow in the central retinal vein. In conjunction with the Department of Medical Physics of the West of Scotland a computer programme has been designed to analyse the complex interaction between the central retinal artery and vein at this site with the supposition that the expansions of the arterial wall have the effect of pumping blood out of the vein. A pathological study of the morphology of the vessels at the lamina cribrosa which detected a constriction in the vein ²⁶⁹ is now being followed by a study examining the vessels in their intraneural portion to allow a correlation of the dynamic properties of the blood flow in these vessels with their structure.

The colour Doppler imaging technique is applicable to a number of ophthalmological conditions and is now being used to examine patients with cranial arteritis ²⁹⁹, carotidocavernous fistula, ocular ischaemic syndrome, intraocular tumours and retinal detachment (unpublished data). In addition, there is potential for the assessment of the effects of a number of pharmacologic agents on the eye, eg., beta blockers ¹¹.

In the condition of central retinal vein occlusion the

contribution of blood viscosity to the aetiology of the condition provides us with possible therapeutic strategies. Already isovolaemic haemodilution has been used to good effect ^{93,94} and a study has been commenced employing venesection in patients with central retinal vein occlusion. The effects of this treatment on blood flow in the eye are being monitored by CDI. In the future the effects of agents which increase the deformability of the red cells (eg., pentoxifyline) could also be assessed. In selected at risk individuals (detected by low venous velocities on CDI) other measures such as anticoagulation may also be tested in an attempt to reduce the incidence of iris neovascularisation ²⁸².

Colour Doppler imaging is an accessible means of assessing the haemodynamics of the eye which has multiple applications in ophthalmology in both the research and clinical setting. In combination with the examination of blood viscosity and haemostasis the method has provided insights into the pathogenetic mechanism of central retinal vein occlusion. It is clinically applicable in this condition as means of estimating the risk of complications providing higher predictive values for the development of iris neovascularisation than fluorescein angiography.

List of Suppliers.

Cross Polarised Filters:	Stereoptical, Nth Kanton Ave, Chicago, Illinois, USA.
Ganzfeld Dome:	Medelec, Woking, UK
Wide Angle Fundus Camera:	Canon, Barenkerkerweg, Amstelveen, Netherlands
Scanning Laser Ophthalmoscope:	Rodenstock (UK), Springhead Rd, Kent, UK
Colour Doppler Imager:	Acuson 128 Acuson, Mountview, California, USA
Personal Computer:	IBM Corp (UK), Greenock, UK
Scottish Home and Health Department:	St Andrew's House, Edinburgh, UK.
Whole blood viscosity and plasma viscosity:	Coulter-Harkness, Coulter ltd, Luton, Beds, UK
Haematocrit:	Hawksley microhaematocrit
Red Cell Aggregation:	Photometric Aggregometer, Myrenne GmbH, Roetgen, Germany
Fibrinogen:	Coag-A-mate X2 Coagulometer Organon Teknika, Cambridge, UK.
Clotting factors VII, VIII, IX and Antithrombin III:	ACL300 Coagulometer Instrumentation Laboratories, Warrington, UK.

Plasminogen Activator Inhibitor:
Quadrtec,
Epsom,
Surrey, UK

Tissue Plasminogen Activator Antigen
Biopool,
Stockholm,
Sweden.

von Willebrand Factor Antigen:
Dako ltd.,
High Wycombe,
Bucks, UK.

Copal Digital Sphygmomanometer:
A and D Company Ltd
Japan

Digilab 30R Pneumatonometer:
Digilab inc.
Cambridge,
Mass, 02139
USA

Yablonski Fundus Lens Ophthalmodynamometer
Varian
Clinitex
Newbury St
Danvers
MA 01923 USA

Abbreviations:

CRVO	Central Retinal Vein Occlusion
ERG	Electroretinography
IOP	Intraocular Pressure
CDI	Colour Doppler Imaging
CBV	Haematocrit Corrected Blood Viscosity
RBV	Relative Blood Viscosity
APC	Activated Protein C
TPA	Tissue Plasminogen Activator
PAI	Plasminogen Activator Inhibitor
VWF	Von Willebrands Factor
PSV	Peak Systolic Velocity
EDV	End Diastolic Velocity (Peak)
Vmax	Maximum Venous Velocity
Vmin	Minimum Venous Velocity (Peak)
VPI	Venous Pulsatility Index
VDU	Visual Display Unit

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